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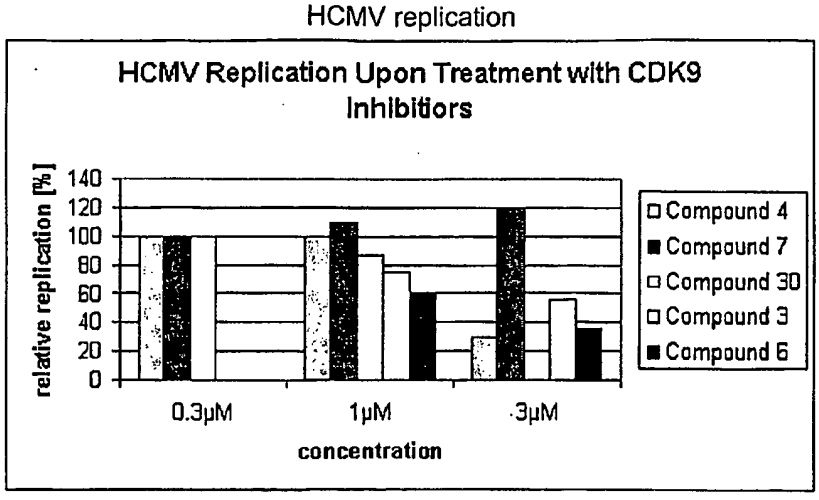
[Continued on next page]

(54) Title: PHARMACEUTICALLY ACTIVE 4,6-DISUBSTITUTED AMINOPYRIMIDINE DERIVATIVES AS MODULATORS OF PROTEIN KINASES



(57) Abstract: The present invention relates to 4,6-disubstituted aminopyrimidine derivatives and/or pharmaceutically acceptable salts thereof, the use of these derivatives as pharmaceutically active agents, especially for the prophylaxis and/or treatment of infectious diseases, including opportunistic diseases, prion diseases, immunological diseases, autoimmune diseases, bipolar and clinical disorders, cardiovascular diseases, cell proliferative diseases, diabetes, inflammation, transplant rejections, erectile dysfunction, neurodegenerative diseases and stroke, and pharmaceutical compositions containing at least one of said 4,6-di substituted aminopyrimidine derivatives and/or pharmaceutically acceptable salts thereof. Furhtermore, the present invention relates to the use of said 4,6-disubstituted aminopyrimidine derivatives as inhibitors for a protein kinase and a medium comprising at least one of said 4,6-disubstituted aminopyrimidine derivatives in an immobilized form and the use of said medium for enriching, purifying and/or depleting nucleotide binding proteins which bind to the immobilized 4,6-disubstituted aminopyrimidine derivatives.

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PHARMACEUTICALLY ACTIVE 4,6-DISUBSTITUTED AMINOPYRIMIDINE DERIVATIVES AS MODULATORS OF PROTEIN KINASES

The present invention relates to 4,6-disubstituted aminopyrimidine derivatives and/or pharmaceutically acceptable salts thereof, the use of these derivatives as pharmaceutically active agents, especially for the prophylaxis and/or treatment of infectious diseases, including opportunistic diseases, prion diseases, immunological diseases, autoimmune diseases, bipolar and clinical disorders, cardiovascular diseases, cell proliferative diseases, diabetes, inflammation, transplant rejections, erectile dysfunction, neurodegenerative diseases and stroke. Furthermore, the present invention is directed towards pharmaceutical composition containing at least one of the 4,6-disubstituted aminopyrimidine derivatives and/or pharmaceutically acceptable salts thereof.

One of the most important and fundamental processes in biology is the division of cells during the cell cycle. This process ensures the controlled production of subsequent generations of cells with defined biological function. It is a highly regulated phenomenon and responds to a diverse set of cellular signals both within the cell and from external sources. Cyclin dependent kinases (CDKs) play a key role in regulating the cell cycle machinery. These complexes consist of two components: a catalytic subunit (the kinase) and a regulatory subunit (the cyclin). To date, eleven kinase subunits have been identified (S. Mani et al., Exp. Opin. Invest. Drugs 2000, 9(8), 1849 – 1870, J.C. Sergere et al., Biochem. Biophys. Res. Commun. 2000, 276, 271 – 277, D. Hu et al, J. Biochem. Chem. 2003, 278(10), 8623 – 8629).

It is known, that CDKs play a role in the regulation of cellular proliferation. Therefore, CDK inhibitors could be useful in the treatment of cell proliferative disorders such as cancer, neuro-fibromatosis, psoriasis, fungal infections, endotoxic shock, transplantation rejection, vascular smooth cell proliferation associated with artheroscelerosis, pulmonary fibrosis, arthritis, glomerulonephritis and post-surgical stenosis and restenosis (U.S. Patent No. 6,114,365).
CDKs are also known to play a role in apoptosis. Therefore CDK inhibitors could be useful in the treatment of cancer; autoimmune diseases, for example systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes; neurodegenerative diseases for example Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral scelrosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration; myelodysplastic syndromes,

aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases; hematological diseases, for example, chronic anemia and aplastic anemia; degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain and for the treatment of cardiovascular diseases (U.S. patent No. 6,107,305 and WO 02/100401). Further it is known, that CDK inhibitors could be used for the treatment of virally induced infectious diseases, such as EBV, HBV, HCV and HIV (WO 02/100401).

Recently, it was described, that HIV-1 replication could be affected by inhibiting CDKs (C. de la Fuenta, Current HIV research, 2003, 1(2), 131 – 152; Y.K. Kim et al., Molecular and Cellular Biology, 2002, 22(13), 4622-4637). Especially CDK9 is reported to be essential for the HIV-1 replication (H.S. Mancebo et al, Genes Dev. 1997, 11(20): 2633-44, O. Flores et al., Proc Natl. Acad. Sci. U S A. 1999, 96(13):7208-13).

Most of the known CDK inhibitors, such as olomoucine, roscovitine, CYC202, purvalanols, indolinones, paullones and 7-hydroxy-staurosporine are focusing on the inhibiton of CDK1 and CDK2 with the goal of antitumor activity (Current opinion in Pharmacalogy, 2003, 3, 1-9). A summary of the known CDK-inhibitors is given by M. Huwe et al. (A. Huwe et al., Angew Chem Int Ed Engl. 2003; 42(19): 2122-38).
Flavopiridol is described as a low-molecular, but unselective inhibitor of CDKs, including CDK9 (W. Filgueira de Azevedo et al., Biochem.and Biophys. Res. Commun. 2002, 293(1), 566-571). Other compounds that were shown to inhibit CDKs are staurosporine, fascaplysin and hymenialdisine.

The use of 4-Aminopyrimidine derivatives as neuroprotective agents is described in WO 02/12198. These compounds generally contain as a basic residue a substituted amine in para position of the anilino part of the molecule and it is stated, that these compounds did not inhibit MEK1/2 kinase activity in P19 neurons.
US Patent No. 3,950,25 describes the use of 4-Amino-6-aryl-pyrimidines as platelet aggregation inhibitors and bronchodilators. US Patent No. 3,478,030 describes the synthesis of benzamide substituted anilino aminopyrimidine derivatives. These compounds are used as potent dilators of coronary arteries. WO 02/79197 describes the use of aryl-substituted 2-aminopyrimidine derivatives

as protein kinase inhibitors, for example as inhibitor of JNK, GSK-3, Src, Lck or CDK2.

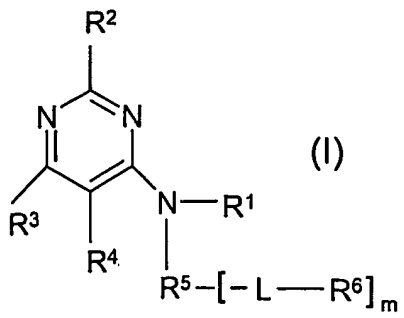
There is a high unmet medical need to develop CDK inhibitors, useful in treating various conditions associated with CDK activation, in particular concerning CDK9 kinase activity, which is associated with HIV replication.

It is object of the present invention to provide compounds and/or pharmaceutically acceptable salts thereof which can be used as pharmaceutically active agents, especially for prophylaxis and/ or treatment of infectious diseases, including opportunistic diseases, prion diseases, immunological diseases, autoimmune diseases, bipolar and clinical disorders, cardiovascular diseases, cell proliferative diseases, diabetes, inflammation, transplant rejections, erectile dysfunction, neurodegenerative diseases and stroke, methods to treat said diseases, as well as compositions comprising at least one of those compounds and/or pharmaceutically acceptable salts thereof as pharmaceutically active ingredients. Another object of the present invention is to provide a medium and a method, which are capable of specifically enriching nucleotide-binding proteins such as protein kinases from a pool of proteins, such as a proteome, a cell lysate or a tissue lysate.

This object is solved by the compounds and/or their pharmaceutically acceptable salt according to independent claim 1, the compounds of the present invention for use as a pharmaceutically active agents according to independent claim 34, the use of the compounds of the present invention for the preparation of a pharmaceutical composition for the prophylaxis and/or treatment of infectious diseases, including opportunistic diseases, prion diseases, immunological diseases, autoimmune diseases, bipolar and clinical disorders, cardiovascular diseases, cell proliferative diseases, diabetes, inflammation, transplant rejections, erectile dysfunction, neurodegenerative diseases and stroke, the use of compounds according to the present invention as inhibitors for a protein kinase according to independent claim 54, the pharmaceutical compositions acording to claim 57, the medium according to claim 58, and the method for enriching, purifying or depleting nucleotide binding proteins according to independent claim 66.

Further advantageous features, aspects and details of the invention are evident from the dependent claims, the description, the examples and the drawings.

The novel 4,6-disubstituted aminopyrimidine compounds according to the present invention are defined by the general formula (I)



(I)

wherein

R^1 is selected from the group comprising:

–H, linear or branched C_1–C_6 substituted or unsubstituted alkyl, linear or branched C_2–C_6 alkenyl or linear or branched C_2–C_6 alkinyl;

R^2 and R^4 are independently selected from the group consisting of:

–H, linear or branched C_1–C_6 substituted or unsubstituted alkyl, linear or branched C_2–C_6 alkenyl, linear or branched C_2–C_6 alkinyl, aryl, –F, –Cl, –Br, –I, –CN, $–NH_2$ or $–NO_2$;

R^3 is selected from the group comprising:

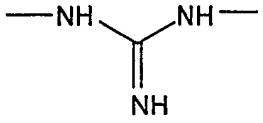
–F, –Cl, –Br, –I, substituted or unsubstituted aryl, substituted or unsubstituted –O–aryl, –NH–aryl, –S–aryl, or substituted or unsubstituted –O–heterocyclyl, –NH–heterocyclyl, –S–heterocyclyl, or substituted or unsubstituted –CH=CH–aryl, or substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl, or substituted or unsubstituted C_3–C_8 cycloalkyl, or $–NH–(CH_2)_n–X$, wherein n is an integer from 0 to 6 and X is selected from –OH, $–NH_2$ or substituted or unsubstituted C_3–C_8 cycloalkyl;

R^5 is selected from the group consisting of:

Substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted C_3–C_8 cycloalkyl, or $–(CH_2)_o–Y$, wherein o is an integer from 0 to 6 and Y represents substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted C_3–C_8 cycloalkyl;

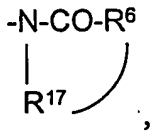
R^6 is selected from the group consisting of:
–H, linear or branched substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted pyrrolidinyl, substituted or unsubstituted C_3–C_8 cycloalkyl, disubstituted cyclohexyl, cyclopentyl, substituted or unsubstituted C_5–C_{12} bicycloalkyl, substituted or unsubstituted adamantyl, $-(CH_2)_q$–group, wherein q is an integer from 1 to 3, under the proviso, if R^6 is selected to be a methylene chain $-(CH_2)_q$–group, R^{17} or R^{19} are selected to be a methylene chain $-(CH_2)_s$–group, wherein s is an integer from 1 to 3 or a $-(CH_2)_t$–A–group, t is an integer from 1 to 3 and A is selected from O or N, respectively, and R^6 and R^{17} or R^6 and R^{19} form together a 5 to 8 membered ring system,
or R^6 represents $-(CH_2)_p$–Z, wherein p is an integer from 0 to 6 and Z is selected from the group comprising:
substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, $-N(R^7R^8)$, wherein R^7 and R^8 represent independently from each other –H, or linear or branched substituted or unsubstituted C_1–C_6 alkyl, or Z is selected from $-(CR^9R^{10}R^{11})$, wherein R^9, R^{10} and R^{11} are independently of each other selected from the group consisting of:
–H, linear or branched substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted aryl or $-N(R^{12}R^{13})$, wherein R^{12} and R^{13} represent independently of each other –H or linear or branched substituted or unsubstituted C_1–C_6 alkyl,
under the proviso, if Z represents $-(CR^9R^{10}R^{11})$ as defined above, p is selected to be an integer from 0 to 6, and
if Z is selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, or $-N(R^7R^8)$ as defined above, p is selected to be an integer from 1 to 6;

L is selected from the group comprising:

–NH–CO–NH–, –NH–CS–NH–, –NH–CO–O–, –CO–, –CO–O–, –SO–, $-SO_2$–, $-SO_3$– or  ;

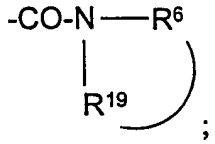
$-NR^{14}$–SO_2–, $-NR^{14}$–SO–,
wherein R^{14} is selected from –H, linear or branched substituted or unsubstituted C_1–C_6 alkyl, $-SO_2$–R^{15}, wherein R^{15} is selected from linear or branched C_1–C_6 alkyl, or R^{14} represents $-(CH_2)_r$–$COOR^{16}$, wherein r is an integer from 0 to 6 and R^{16} is selected from –H or linear or branched substituted or unsubstituted C_1–C_6 alkyl,

$-NR^{17}-CO-$,
wherein R^{17} is selected from –H, linear or branched substituted or unsubstituted C_1–C_6 alkyl, or a $-(CH_2)_s$–group, wherein s is an integer from 1 to 3, and
wherein R^6 and R^{17} represent both a methylene chain group, R^6 and R^{17} may form together a 5 to 8 membered ring system:



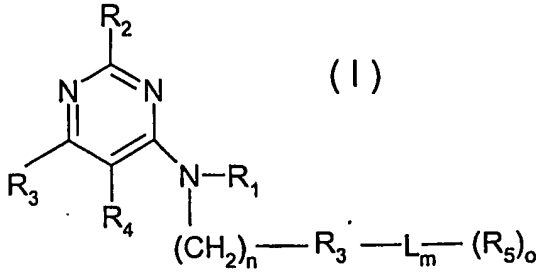
$-SO_2-NR^{18}-$,
wherein R^{18} is selected from –H, or linear or branched substituted or unsubstituted C_1–C_6 alkyl,

$-CO-NR^{19}-$,
wherein R^{19} is selected from –H, linear or branched substituted or unsubstituted C_1–C_6 alkyl, or a $-(CH_2)_t$–A–group, wherein t is an integer from 1 to 3 and A is selected from N or O, and wherein if R^6 represents a $-(CH_2)_q$–group and R^{19} represents a $-(CH_2)_t$–A–group,

R^6 and R^{19} may form together a 5 to 8 membered ring system  ;

and **m** is selected to be 0 or 1,
and/or stereoisomeric forms and/or pharmaceutically acceptable salts thereof.

Preferred are compounds having the general formula (I):



(I)

wherein

each R_1 represents independently R_3, R_5, –H, linear or branched substituted or unsubstituted C_1–C_6 alkyl, linear or branched C_2–C_6 alkenyl or linear or branched C_2–C_6 alkinyl or adamantyl,

R_2 and R_4 are independently selected from the group consisting of:

R_3, R_5, –H, –CN, $-NH_2$, $-NO_2$, linear or branched substituted or unsubstituted C_1 – C_6 alkyl, linear or branched C_2 – C_6 alkenyl or C_2 – C_6 linear or branched alkinyl;

R_3 and R_3' are independently selected from the group consisting of:

a) halogen, represented by –F, –Cl, –Br or –I,

b) C_3 – C_8 cycloalkyl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7',

c) C_4 – C_{12} bicyclo-alkyl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7',

d) aryl , which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7',

e) X–aryl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7' and wherein X is independently selected from –O–, –NH–, –S–, linear or branched $-CH_2-(C_2-C_6$ alkyl)-group, linear or branched $-CH_2-(C_2-C_6$ alkenyl)-group , which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7',

f) partially or fully saturated 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this heterocyclic ring can be fused to another 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R'_7,

or a 5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this heteroaryl ring can be fused to another partially or fully saturated 5 or 6 membered heterocyclic group, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7' or to a 5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R'_7;

g) guanidinyl group, optionally substituted by at least one group R_5 or

h) $-Y-(CH_2)_p-Z$ group, wherein Y represents O, S or NR_5 and Z represents R_5, $-OR_5$, $-N(R_5)_2$ or $-COOR_5$,

wherein in the cases, that the group R_3' represents one of the groups cited under a), g) or h) the indices m and o of the $-(L)_m-(R_5)_o$-group are selected to be 0,

R_5 is independently selected from the group consisting of:

– H, R_1, R_2, R_3, R_4, $-(CH_2)_q-COOR_1$, $-CH=CH-COOR_1$,
$-C(R_1)_2N(R_1)_2$, $-(CH_2)_rN(R_1)_2$, $-NR_1-COOR_1$ or $-C(R_1)_3$,

R_6 and R_6' are independently selected from the group consisting of:
R_1, R_2, R_4, R_5, L–H, –H, $-OR_1$, $-N(R_1)_2$, $-C(R_1)_3$, $-CH(R_1)_2$, or $-CH_2R_1$;
R_7 and R_7' represent independently from each other R_6 and R_6';

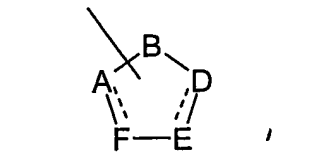
L is selected from the group comprising:
$-NR_5-SO_2-$, $-NR_5-CO-(CH_2)_s-$, –NH–CO–NH–, $-CO-NR_5-$, $-SO_2-NR_5-$ or –NH– under the proviso, that if m is selected to be 1, o is selected to be 1 as well,

m is independently selected to be 0 or 1,
n is independently selected to be an integer from 0 to 6,
o is independently selected to be 0 or 1,
p, q, r and s are independently from each other an integer from 0 to 6
and/or stereoisomeric forms and/or pharmaceutically acceptable salts thereof.

In formula (I) shown above, the group R_3'-L_m-$(R_5)_o$ is to be understood in the sense, that the group denoted by R_3' is optionally substituted by a group -L_m-$(R_5)_o$. This means that if R_3' is for instance an aryl group, such as phenyl, one of the hydrogen atoms bonded to the aryl group is exchanged by a -L_m-$(R_5)_o$ group.

The group aryl as used in items d) and e) of the definition of the groups R_3 and R_3', preferably describes an aryl group independently selected from the group consisting of phenyl, biphenyl or naphthyl.

In a preferred embodiment of the compounds according to the present invention the rings defined under f) of the definition of the groups R^3 and $R^{3'}$ are independently selected to be



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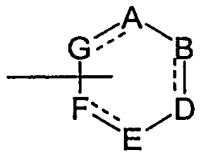

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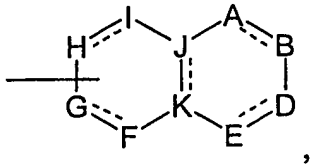

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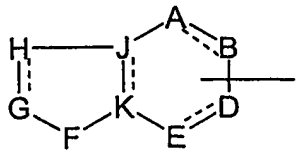

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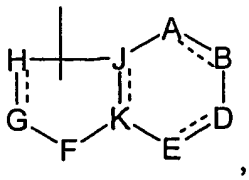

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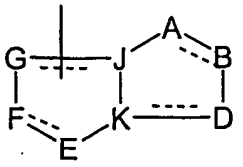


,

wherein

A, B, D, E, F, G ,H and I represent independently of each other:

CR_6, $C(R_6)_2$, N, NR_6, O or SR_6

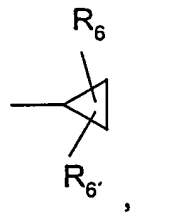
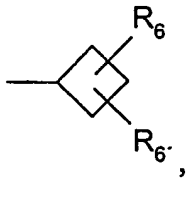
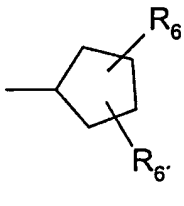
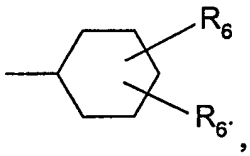
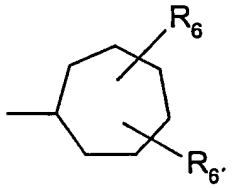
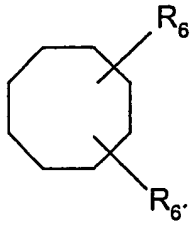
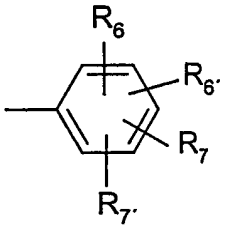
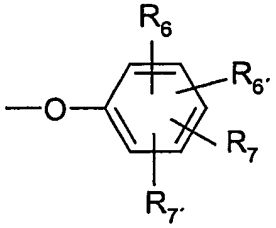
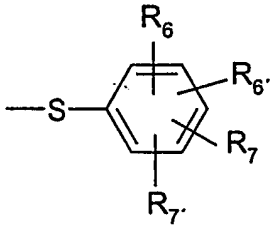
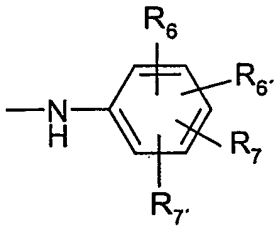
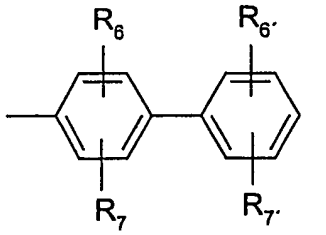
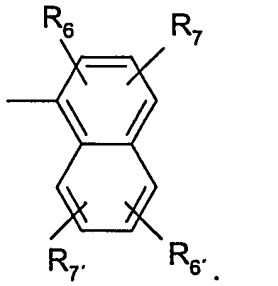
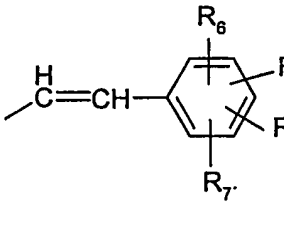
J and K are independently from each other: C or N, under the proviso that O–O and S–S bonds are excluded and that at least one of the ring atoms in the heterocycle is N, S or O,

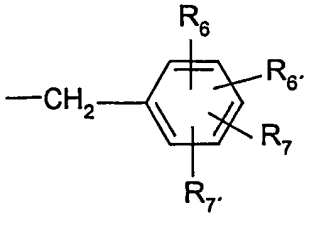
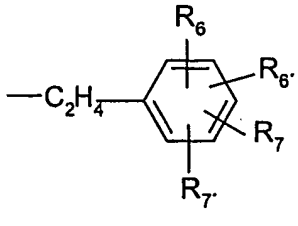
and each ⎓ represent independently from each other a single or a double bond under the proviso that one of the groups R_6 comprised in A, B, D, E, F, G H, I, J and K is exchanged with a $-(L)_m-(R_5)_o$-group.

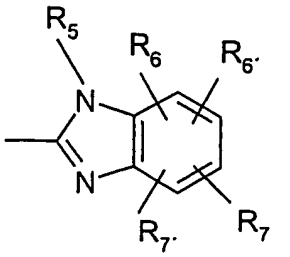
In a further preferred embodiment of the compounds according to the invention R_1, R_2 and R_4 represent independently of each other R_3, R_5, –H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH_2-C(CH_3)_3$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$, $-CH=CH_2$, $-C\equiv CH$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C\equiv C-CH_3$, $-CH_2-C\equiv CH$, $-C_2H_4-CH=CH_2$, $-CH=CH-C_2H_5$, $-CH=C(CH_3)_2$, $-CH_2-CH=CH-CH_3$, $-CH=CH-CH=CH_2$, $-C_2H_4-C\equiv CH$, $-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-CH_3$, $-C\equiv C-CH=CH_2$, $-CH=CH-C\equiv CH$, $-C\equiv C-C\equiv CH$, $-C_3H_6-CH=CH_2$, $-CH=CH-C_3H_7$, $-C_2H_4-CH=CH-CH_3$, $-CH_2-CH=CH-C_2H_5$, $-CH_2-CH=CH-CH=CH_2$, $-CH=CH-CH=CH-CH_3$, $-CH=CH-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$, $-CH=CH-C(CH_3)=CH_2$, $-CH_2-CH=C(CH_3)_2$, $-C(CH_3)=C(CH_3)_2$, $-C_3H_6-C\equiv CH$, $-C\equiv C-C_3H_7$, $-C_2H_4-C\equiv C-CH_3$, $-CH_2-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-CH=CH_2$, $-CH_2-CH=CH-C\equiv CH$, $-CH_2-C\equiv C-C\equiv CH$, $-C\equiv C-CH=CH-CH_3$, $-CH=CH-C\equiv C-CH_3$, $-C\equiv C-C\equiv C-CH_3$, $-C\equiv C-CH_2-CH=CH_2$, $-CH=CH-CH_2-C\equiv CH$, $-C\equiv C-CH_2-C\equiv CH$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$, $-CH=CH-C(CH_3)=CH_2$, –

$C(CH_3)=CH-C\equiv CH$, $-CH=C(CH_3)-C\equiv CH$, $-C\equiv C-C(CH_3)=CH_2$,
$-C_4H_8-CH=CH_2$, $-CH=CH-C_4H_9$, $-C_3H_6-CH=CH-CH_3$,
$-CH_2-CH=CH-C_3H_7$, $-C_2H_4-CH=CH-C_2H_5$, $-CH_2-C(CH_3)=C(CH_3)_2$,
$-C_2H_4-CH=C(CH_3)_2$, $-C_4H_8-C\equiv CH$, $-C\equiv C-C_4H_9$, $-C_3H_6-C\equiv C-CH_3$,
$-CH_2-C\equiv C-C_3H_7$, $-C_2H_4-C\equiv C-C_2H_5$; and

R_3 and $R_{3'}$ represent independently of each other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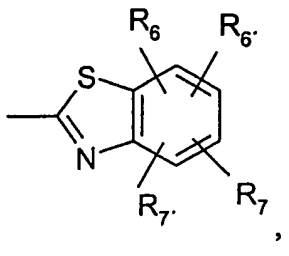
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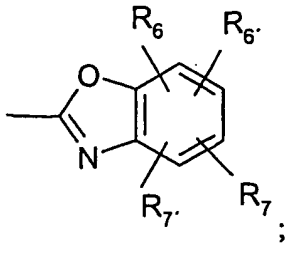
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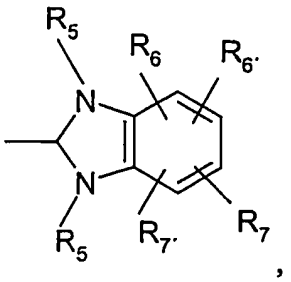
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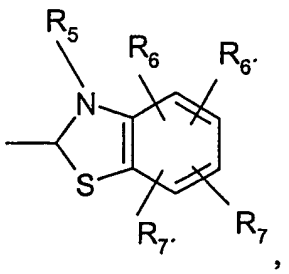
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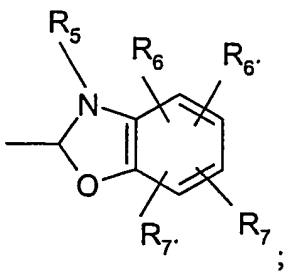
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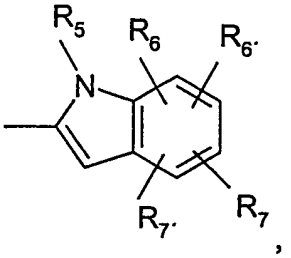
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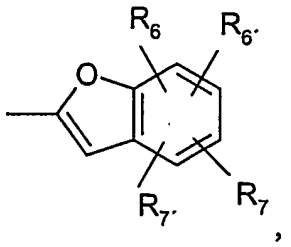
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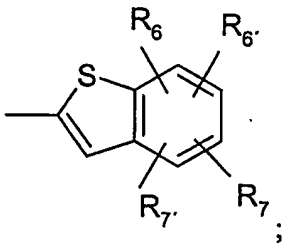
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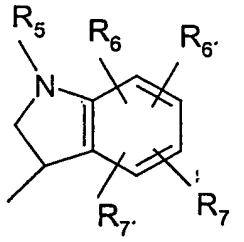
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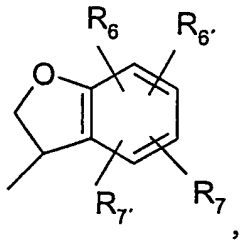
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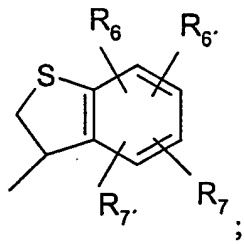
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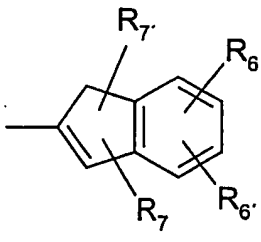
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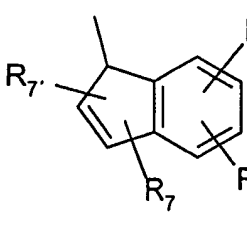
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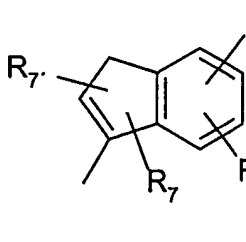
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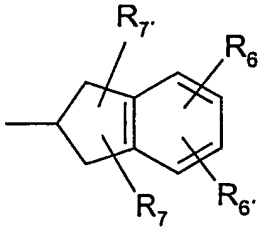
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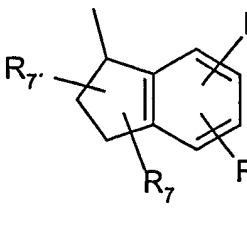
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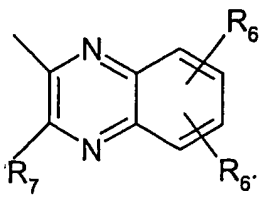

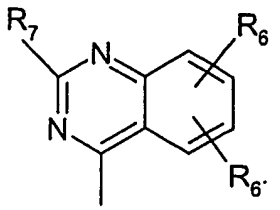

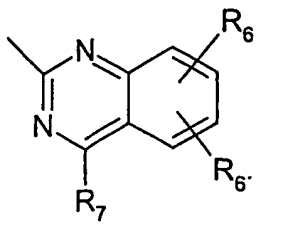

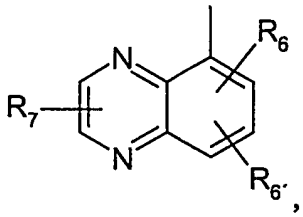

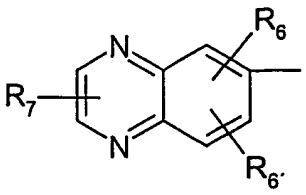

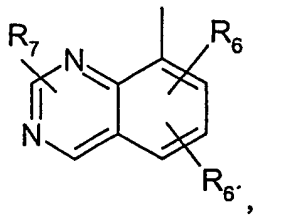

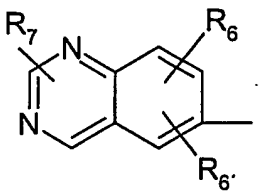

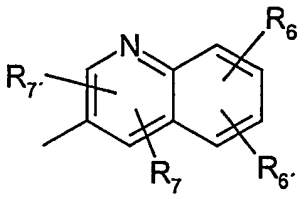

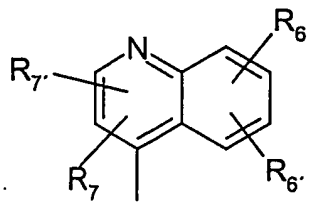

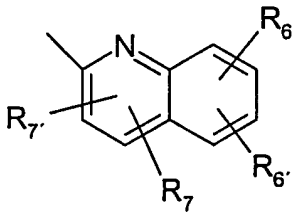

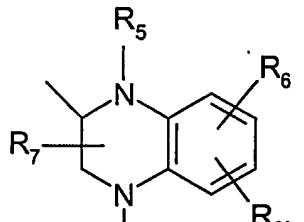

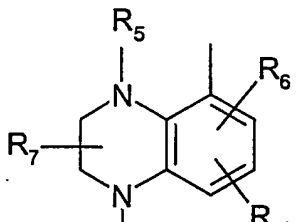

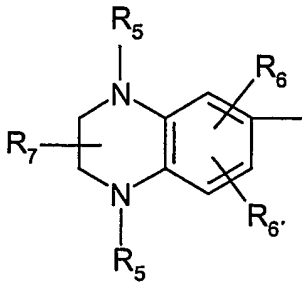

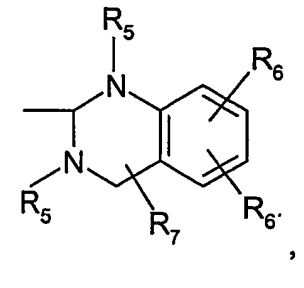

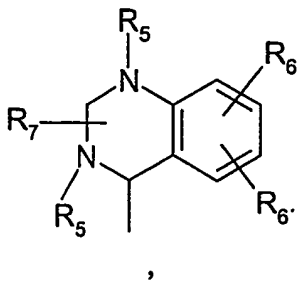

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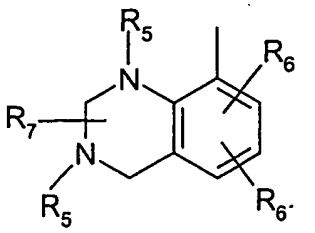

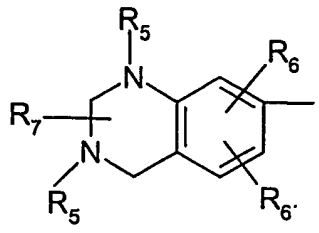

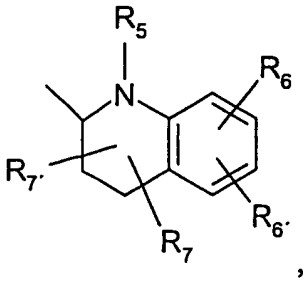

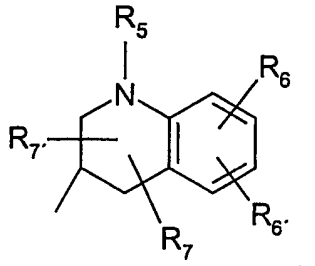

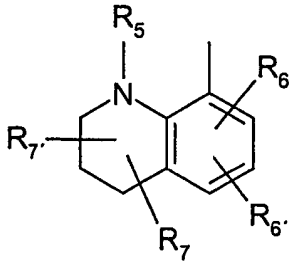

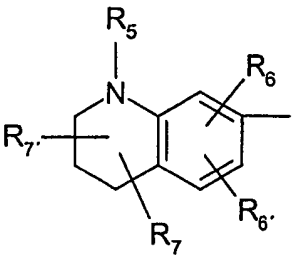

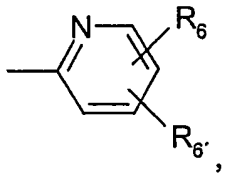

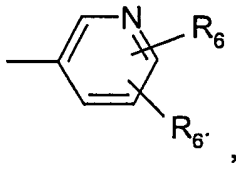

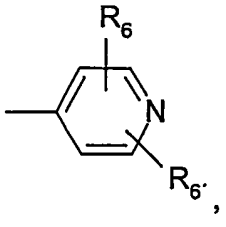

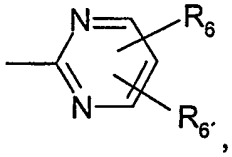

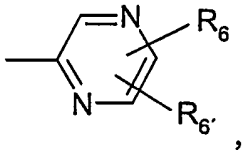

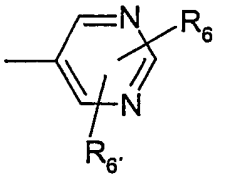

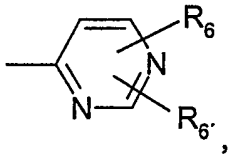

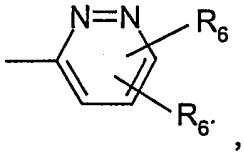

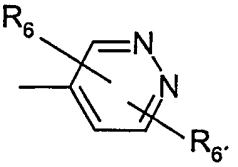

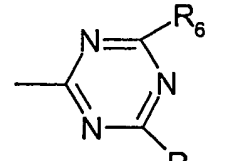

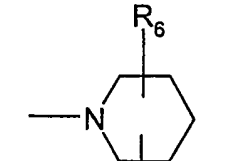

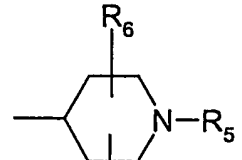

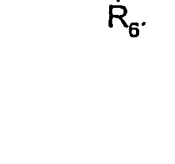

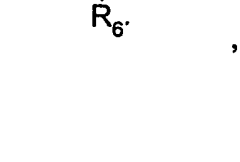

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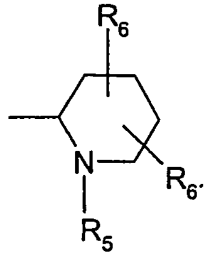
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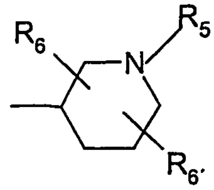
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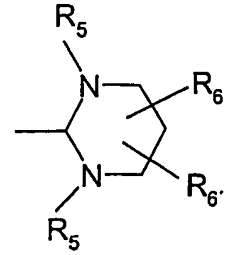
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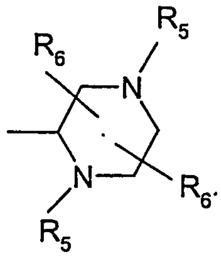
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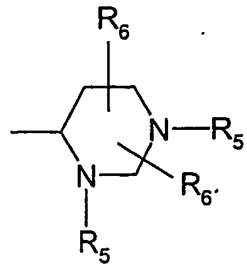
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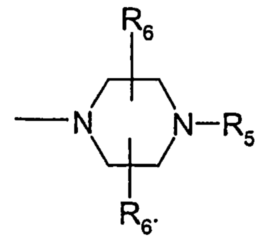
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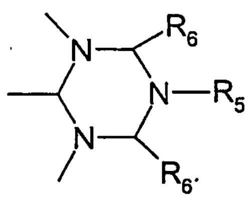
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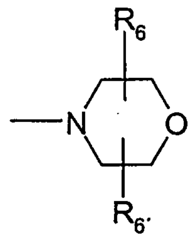
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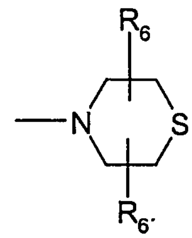
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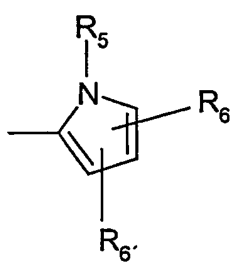
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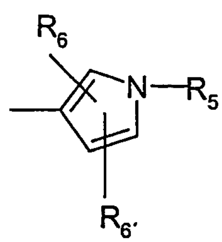
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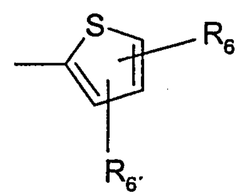
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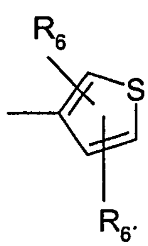
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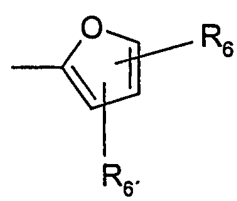

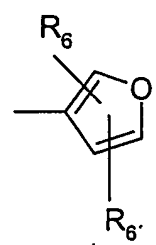
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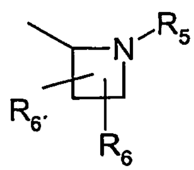
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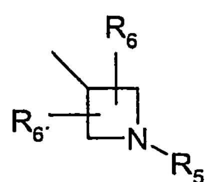
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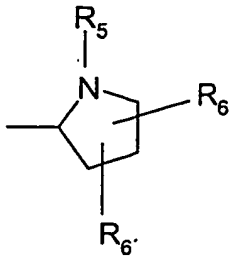
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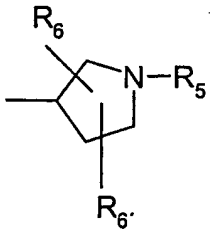
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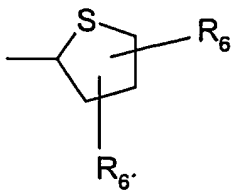
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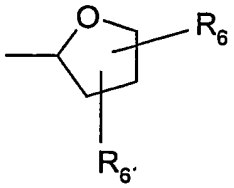
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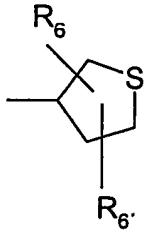
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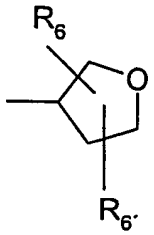
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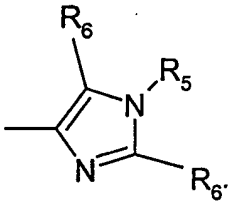
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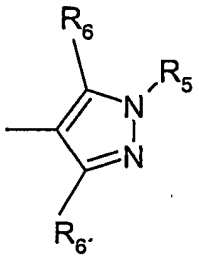
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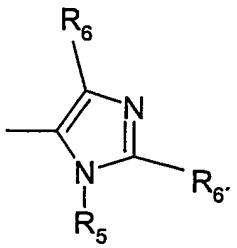
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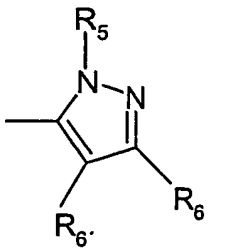
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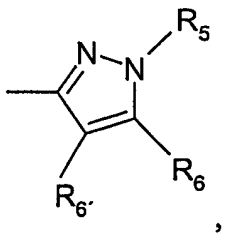
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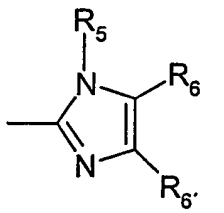
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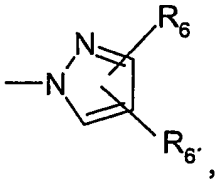
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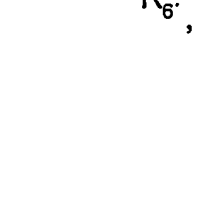
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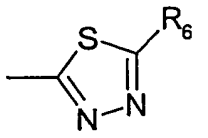
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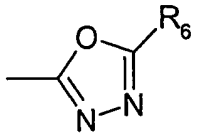
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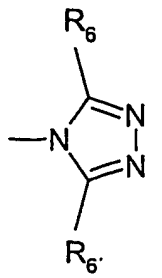
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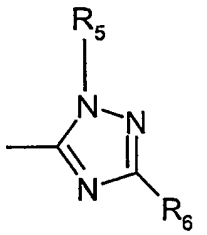
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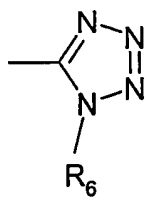
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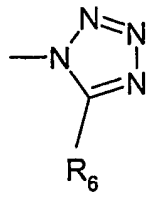
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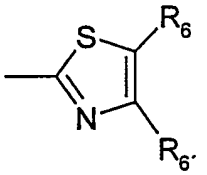
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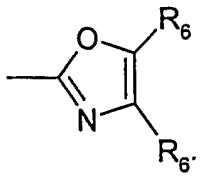
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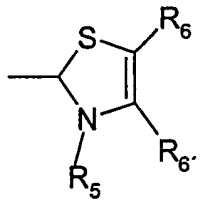
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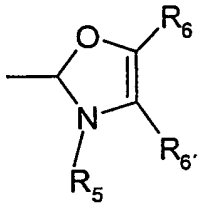
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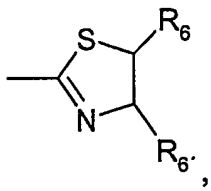
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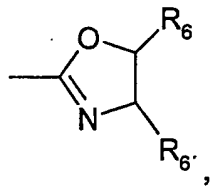
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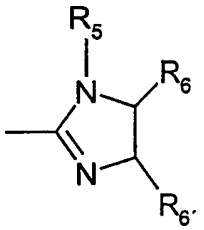
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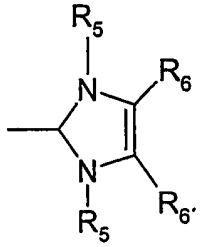
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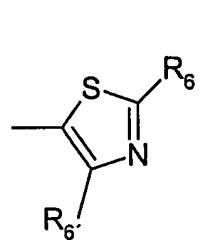
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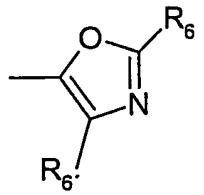
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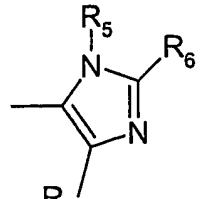
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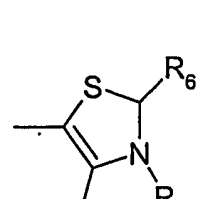
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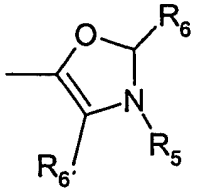
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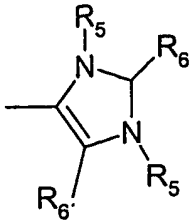
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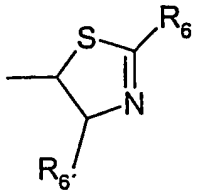
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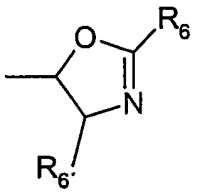
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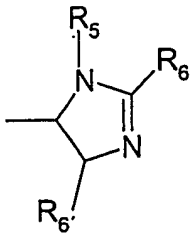
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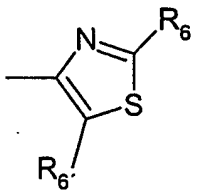
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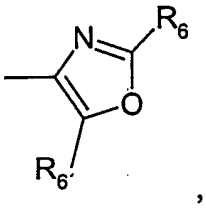
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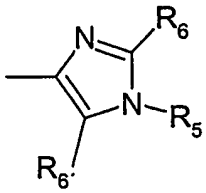
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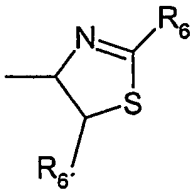
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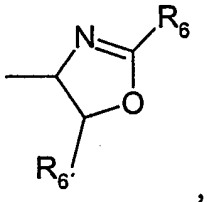
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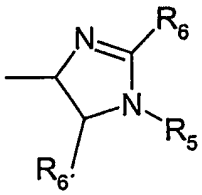
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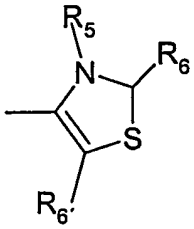
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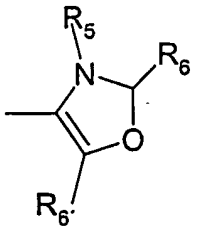
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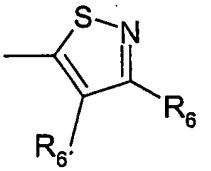
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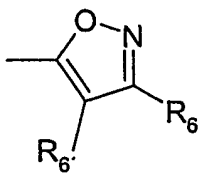
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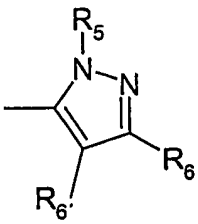
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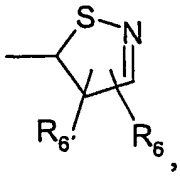
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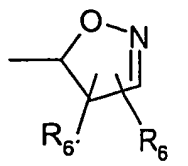
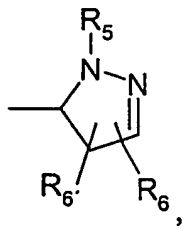
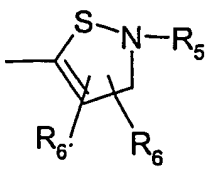
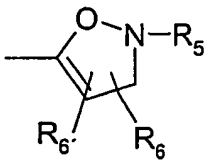
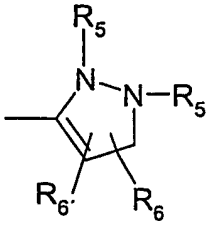
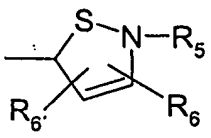
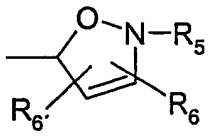
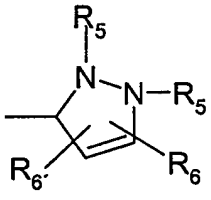
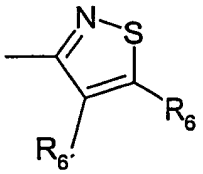
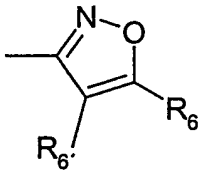
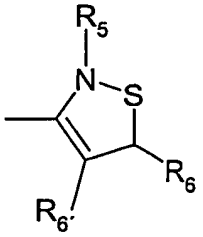
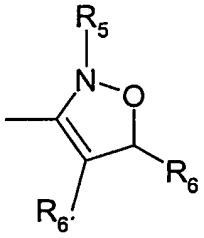
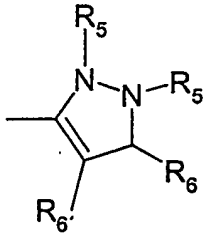
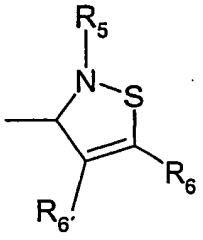
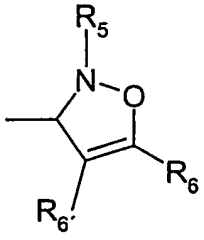
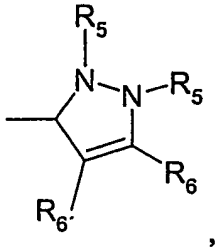
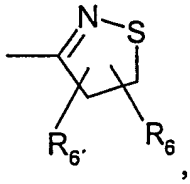
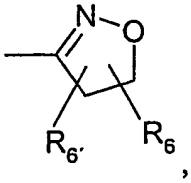
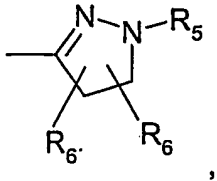

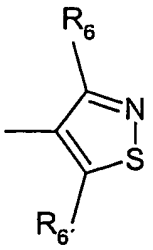
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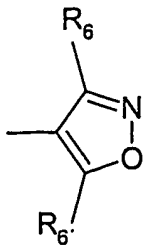
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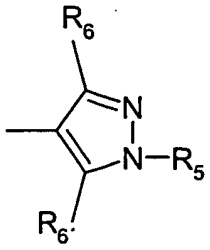
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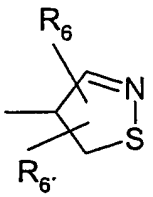
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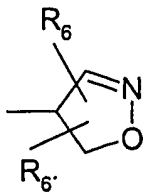
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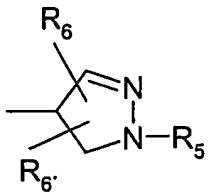
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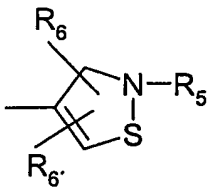
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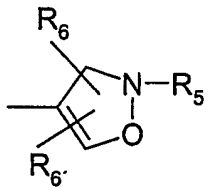
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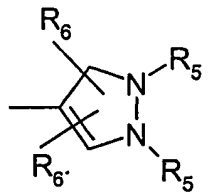
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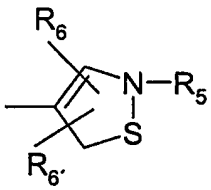
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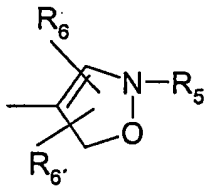
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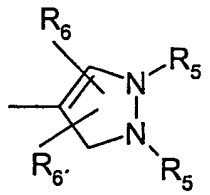
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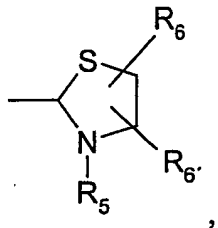
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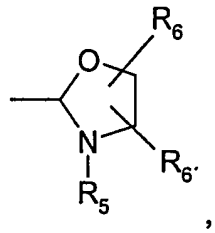
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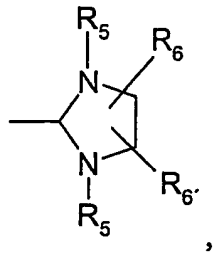
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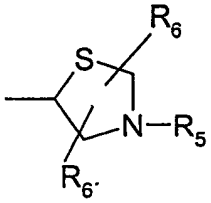
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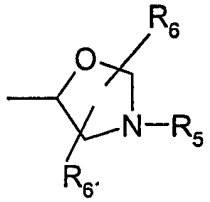
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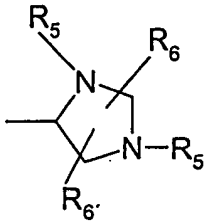
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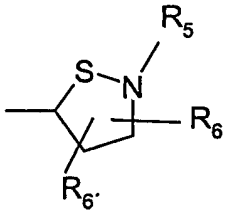
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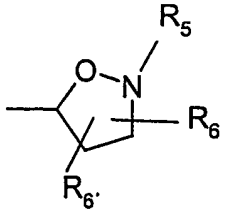
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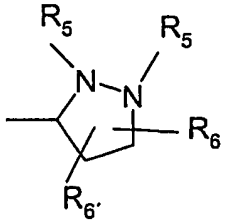
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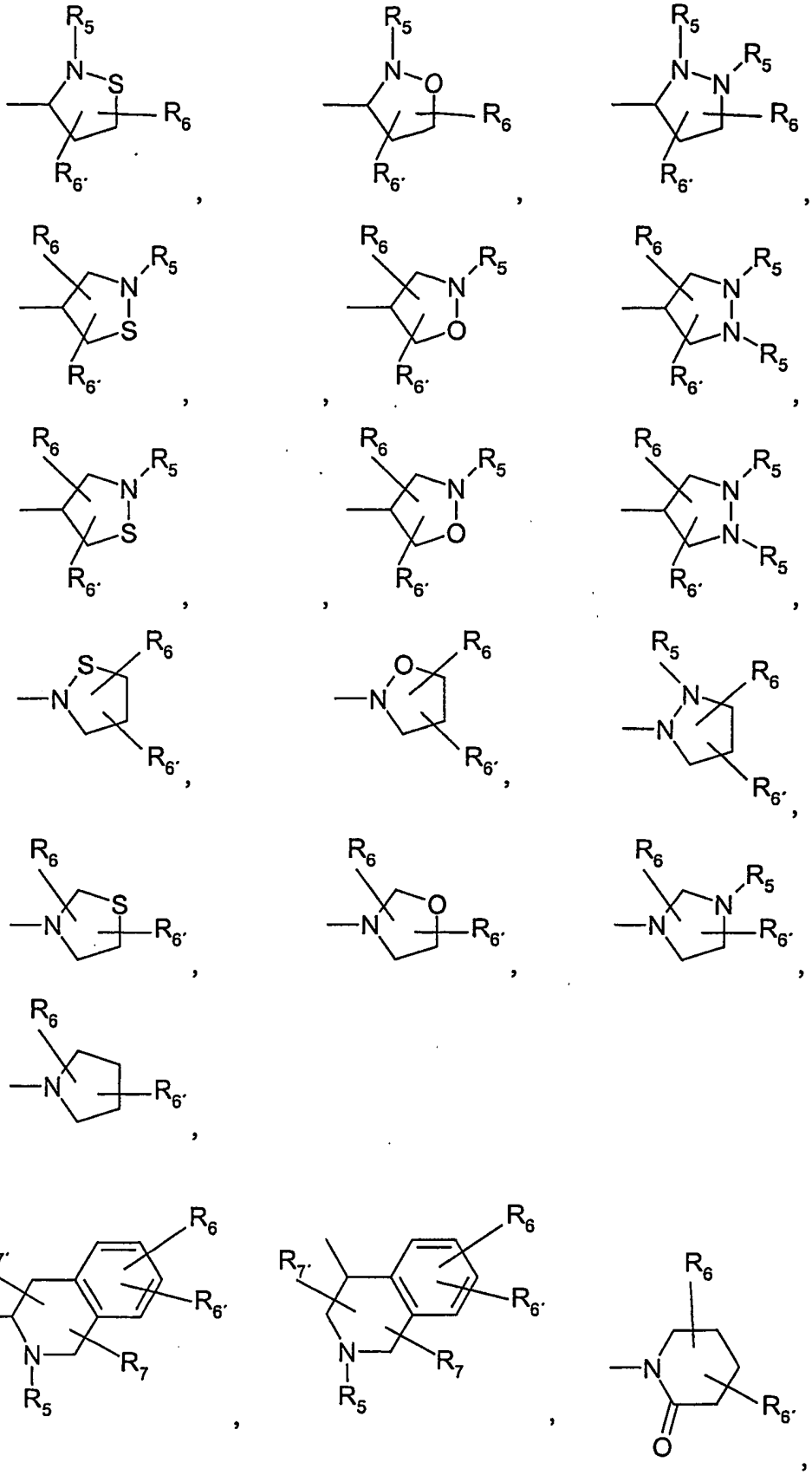
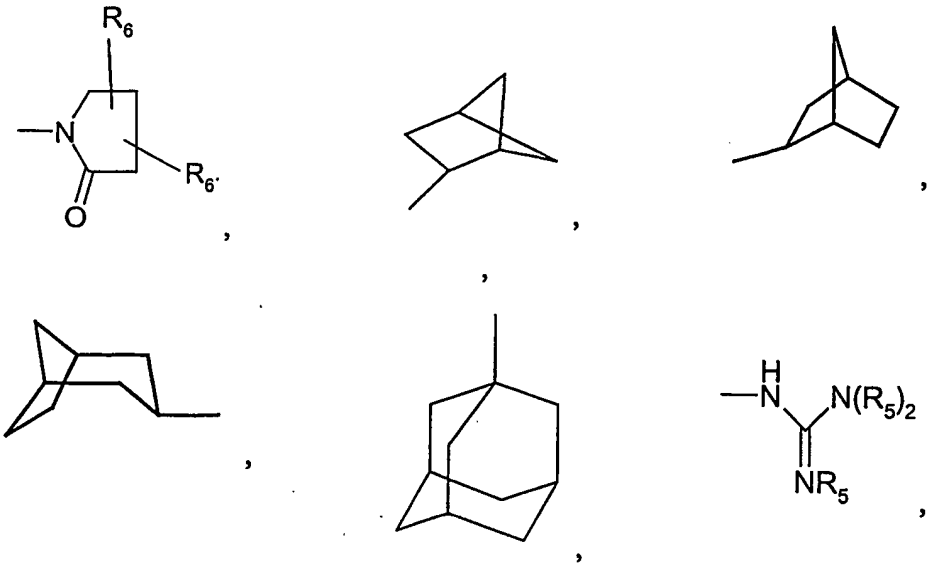




and R_5, R_6, R_6', R_7, R_7' L, X, Y, Z , n, m, o, p, q, r and s have the meanings as defined before.

In yet a further preferred embodiment of the compounds according to the present invention R_1 represents –H or linear or branched $C_1 - C_6$ alkyl, linear or branched $C_2 - C_6$ alkenyl or linear or $C_2 - C_6$ branched alkinyl,
R_2 and R_4 represent independently of each other –H or linear or branched $C_1 - C_6$ alkyl, linear or branched $C_2 - C_6$ alkenyl, linear or branched $C_2 - C_6$ alkinyl, $-NH_2$, $-NO_2$, –CN, R_3 or R_5;
R_3, R_3', R_5, R_6, R_6', R_7, R_7' L, X, Y, Z , n, m, o, p, q, r and s have the meanings as defined above.

In a further preferred embodiment of the compounds according to the present invention R_1 represents –H or linear or branched $C_1 - C_6$ alkyl,
R_2 and R_4 represent independently of each other –H, $-NH_2$, linear or branched $C_1 - C_6$ alkyl,
R_3 and R_3' are independently selected from the group comprising of:
Halogen, X-aryl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', aryl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; partially or fully saturated 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this heterocyclic ring can be fused to another 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7',
5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this heteroaryl ring can be fused to another partially

or fully saturated 5 or 6 membered heteroccyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7' or to a 5 or 6 membered heteroaryl ring, which is optionally substituted at least one of the groups R_6, R_6', R_7 or R_7',

guanidinyl group, optionally substituted by at least one R_5 group or a $-Y-(CH_2)_p-Z$ group, wherein X, Y, Z and p have the meanings as defined in claim 1 and

R_5, R_6, R_6', R_7, R_7', L, n, m, o, q, r and s have the meanings as defined above.

In yet another preferred embodiment of the compounds of the present invention R_1 represents –H or linear or branched $C_1 - C_6$ alkyl,

R_2 and R_4 represent independently of each other –H, $-NH_2$ or linear or branched $C_1 - C_6$ alkyl,

R_3 and R_3' are independently selected from the group comprising of:

Halogen, X-aryl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', aryl , which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', partially or fully saturated 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this heterocyclic ring can be fused to another 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7',

5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this heteroaryl ring can be fused to another partially or fully saturated 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7' or to a 5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7',

guanidinyl group, optionally substituted by at least one R_5 group or a $-Y-(CH_2)_p-Z$ group, wherein X, Y, Z and p have the meanings as defined in claim 1;

L represents $-NR_5-SO_2-$, $-NR_5-CO-(CH_2)_s-$, $-NH-CO-NH-$, $-CO-NR_5-$ or $-SO_2-NR_5-$,

R_5, R_6, R_6', R_7, R_7' n, m, o, q, r and s have the meanings as defined above.

In yet another preferred embodiment of the compounds according to the present invention R_1 represents –H or linear or branched $C_1 - C_6$ alkyl;

R_2 and R_4 represent independently of each other –H or NH_2;

R_3 and R_3' are independently selected from the group comprising of:

Halogen, X-aryl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', aryl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', partially or fully saturated 5 or 6 membered heterocyclic ring which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this ring can be fused to another 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7',
5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this ring can be fused to another partially or fully saturated 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7' or to a 5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7',
guanidinyl group, optionally substituted by at least one R_5 group or a $-Y-(CH_2)_p-Z$ group, wherein X, Y, Z and p have the meanings as defined in claim 1;

L represents $-NR_5-SO_2-$, $-NR_5-CO-(CH_2)_s-$, $-NH-CO-NH-$, $-CO-NR_5-$ or $-SO_2-NR_5-$,

R_5 is selected from the group consisting of:
linear or branched C_1 – C_6 alkyl, C_3 – C_8 cycloalkyl , which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; C_4 – C_{12} bicycloalkyl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7',
aryl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', $-CH_2$ –aryl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', partially or fully saturated 5 or 6 membered heterocyclic ring, which is optionally substituted by R_6, R_6', R_7 or R_7'; this ring can be fused to another 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', 5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this ring can be fused to another partially or fully saturated 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 and R_7' or to a 5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', $-(CH_2)_q-COOR_1$, wherein R_1 represents – H or a linear or branched C_1 – C_6 alkyl, $-(CH_2)_r-N(R_1)_2$, wherein R_1 represents independently – H or a linear or branched C_1 – C_6 alkyl, $-(CR_1)_2-N(R_1)_2$, wherein R_1 represents independently – H or a linear or branched C_1 – C_6 alkyl or $-C(R_1)_3$, wherein R1 represents independently – H, a linear or branched C_1 – C_6 alkyl or an aryl group, which is optionally substituted by R_6, R_6', R_7 and R_7';

R_6, R_6', R_7, R_7' n, m, o, p, q, r and s have the meanings as defined above.

In yet another preferred embodiment of the compounds according to the present invention, R_1 represents –H or linear or branched C_1 – C_6 alkyl,
R_2 and R_4 represent independently of each other –H or NH_2,
R_3 and R_3' are independently selected from the group comprising of:
Halogen, X-aryl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', aryl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', partially or fully saturated 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this heterocyclic ring can be fused to another 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7',
5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this heteroaryl ring can be fused to another partially or fully saturated 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7' or to a 5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'or a $–Y–(CH_2)_p–Z$ group, wherein X, Y, Z and p have the meanings as defined in claim 1;
L represents $–NR_5–SO_2–$, $–NR_5–CO–(CH_2)_n–$, –NH–CO–NH–, $–CO–NR_5–$ or $–SO_2–NR_5$ –

R_5 is selected from the group comprising:

linear or branched C_1 – C_6 alkyl, , aryl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', partially or fully saturated 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this heterocyclic ring can be fused to another 5 or 6 membered heterocylic ring, which is optionally substituted by R_6, R_6', R_7 or R_7',
5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this heteroaryl ring can be fused to another partially or fully saturated 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7' or to a 5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', C_3 – C_8 cycloalkyl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7' or C_4-C_{12} bicycloalkyl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7';

R_6, R_6', R_7 and R_7' represent independently of each other:
–H, –F, –Cl, –Br, –I, R_1, $–OR_1$, $–N(R_1)_2$, –CH=CH $–COOR_1$, $–(CH_2)_qCOOR_1$, or a $–O–(CH_2)_t$ –aryl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', wherein in these cases, R_1 is independently

selected from –H or linear or branched C_1 – C_6 alkyl and t is selected to be an integer from 0 to 6,

n, m, o, p, q, r and s have the meanings as defined above.

In yet another preferred embodiment of the present invention R_6, R_6', R_7, R_7' represent independently of each other –H, linear or branched C_1 – C_6 alkyl, $-OR_1$, $-O-(CH_2)_s$ –aryl group, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; $-N(R_1)_2$, $-CH=CH-COOR_1$ $-(CH_2)_qCOOR_1$, wherein in these cases, R_1 represents independently –H or linear or branched C_1 – C_6 alkyl.

In a further embodiment of the compounds according to the present invention,
R_1 represents –H or linear or branched C_1 – C_6 alkyl,
R_2 and R_4 are independently selected from –H or $-NH_2$.

In yet another embodiment of the compounds of the present invention as defined by general formula (I),

each R_1 independently represents –H, linear or branched C_1 – C_6 alkyl, linear or branched C_2– C_6 alkenyl or linear or branched C_2– C_6 alkinyl or benzyl, preferably –H, or linear or branched C_1 – C_6 alkyl,

R_2 and R_4 are independently selected from the group consisting of:
–H, –CN, , $-NH_2$, $-NO_2$, linear or branched C_1 – C_6 alkyl, linear or branched C_2 – C_6 alkenyl or C_2 – C_6 linear or branched alkinyl, and preferably are independently selected from -H or $-NH_2$,

R_3 is selected from the group consisting of halogen, pyridinly, thienyl, phenyl and biphenyl, preferably phenyl, which are optionally substituted by at least one of the groups R_6, R_6', R_7, R_7', R_6, wherein R_6, R_6', R_7, R_7' are preferably selected from halogen, such as -F, -Cl, -Br, or I, $-OR_1$, $-N(R_1)_2$, wherein in these groups each R_1 is preferably independently selected from –H or linear or branched C_1 – C_6 alkyl or benzyl,

n is selected to be 0,

m is 0 or 1, preferably 1,

o is 0 or 1, preferably 1,

R_3' is phenyl, optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', wherein R_6, R_6', R_7, R_7' are preferably selected from halogen, such as -F, -Cl, -Br, or I, $-OR_1$, $-N(R_1)_2$, wherein in these groups each R_1 is preferably independently selected from –H or linear or branched C_1 – C_6 alkyl,

L is -NH-CO-$(CH_2)_s$-, wherein s is preferably 0 or 1, or -NH-SO_2-, and preferably is -NH-CO-,

and

R_5 is selected from the group consisting of:

a partially or fully saturated 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this heterocyclic ring can be fused to another 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7, wherein R_6, R_6', R_7, R_7' in these heterocyclic rings are preferably selected from halogen, such as -F, -Cl, -Br, or I, -OR_1, -$N(R_1)_2$, wherein in these groups each R_1 is preferably independently selected from –H or linear or branched C_1 – C_6 alkyl, and wherein R_5 is preferably selected from the group consisting of azetidinyl, pyrrolidinyl, or piperidinyl, each of these heterocycles optionally substituted in the above indicated manner,

a 5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7'; this heteroaryl ring can be fused to another partially or fully saturated 5 or 6 membered heterocyclic group, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7' or to a 5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7; wherein R_6, R_6', R_7, R_7' in these rings are preferably selected from halogen, such as -F, -Cl, -Br, or I, -OR_1, -$N(R_1)_2$, wherein in these groups each R_1 is preferably independently selected from –H or linear or branched C_1 – C_6 alkyl, and wherein R_5 is preferably selected from the group consisting of benzoxazoly, benzimidazolyl, chinolinyl, imidazoly, benzothiazolyl, 1, 2, 3, 4,-Tetrahydro-isoquinolinyl, or pyridinyl, each of these groups optionally being substituted in the above indicated manner,

phenyl, optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', wherein R_6, R_6', R_7, R_7' are preferably selected from halogen, such as -F, -Cl, -Br, or I, -OR_1, -$N(R_1)_2$, wherein in these groups each R_1 is preferably independently selected from –H or linear or branched C_1 – C_6 alkyl, or

C_1-C_6-alkyl or a C_3-C_8-cycloalkyl, which is optionally substituted by at least one of the groups R_6, R_6', R_7 or R_7', wherein R_6, R_6', R_7, R_7' are preferably selected from halogen, such as -F, -Cl, -Br, or I, -OR_1, -$N(R_1)_2$, wherein in these groups each R_1 is preferably independently selected from –H or linear or branched C_1 – C_6 alkyl.

In a further embodiment of the present invention, the compound of the present invention defined by general formula (I) represents a chiral compound. The compound can be a racemate or a R or a S enantiomer.

As used in the present invention the terms linear or branched C_1–C_8 alkyl, linear or branched C_2–C_6 alkenyl or linear or branched C_2–C_6 alkinyl are meant to include the following alkyls, alkenyls or alkinyls:

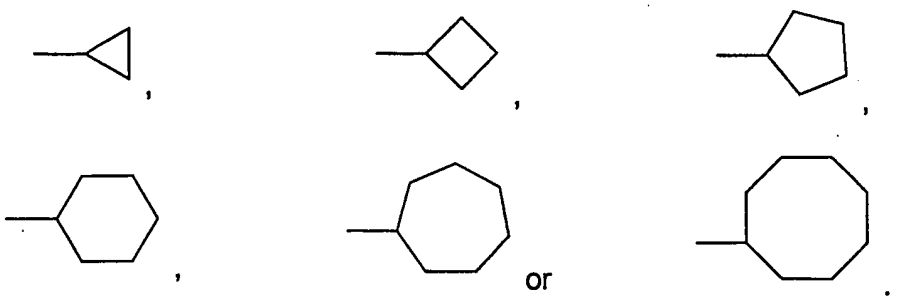
$-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$, $-(CH_2)_6-CH_3$, $-CH(CH_3)-(CH_2)_4-CH_3$, $-(CH_2)_2-CH(CH_3)-(CH_2)_2-CH_3$, $-(CH_2)_3-CH(CH_3)-C_2H_5$, $-(CH_2)_4-CH(CH_3)_2$, $-C(CH_3)_2-(CH_2)_3-CH_3$, $-CH_2-C(CH_3)_2-(CH_2)_2-CH_3$, $-(CH_2)_2-C(CH_3)_2-C_2H_5$, $-(CH_2)_4-CH(CH_3)_2$, $-(CH_2)_3-C(CH_3)_3$, $-CH(C_2H_5)-(CH_2)_3-CH_3$, $-(CH_2)_3-CH(C_2H_5)-CH_3$, $-C(C_2H_5)_3$, $-CH_2-C(C_2H_5)_2-CH_3$, $-(CH_2)_2-CH(C_2H_5)_2$, $-CH(C_3H_7)-(CH_2)_2-CH_3$, $-CH_2-CH(C_3H_7)-C_2H_5$, $-(CH_2)_2-CH(C_3H_7)-CH_3$, $-(CH_2)_7-CH_3$, $-CH(CH_3)-(CH_2)_5-CH_3$, $-(CH_2)_2-CH(CH_3)-(CH_2)_3-CH_3$, $-(CH_2)_3-CH(CH_3)-(CH_2)_2-CH_3$, $-(CH_2)_4-CH(CH_3)-C_2H_5$, $-(CH_2)_5-CH(CH_3)_2$, $-(CH_2)_4-C(CH_3)_3$, $-CH(C_2H_5)-(CH_2)_4-CH_3$, $-(CH_2)_2-CH(C_2H_5)-(CH_2)_2-CH_3$, $-(CH_2)_3-CH(C_2H_5)_2$, $-CH(C_3H_7)-(CH_2)_3-CH_3$, $-CH_2-CH(C_3H_7)-(CH_2)_2-CH_3$, $-(CH_2)_2-CH(C_3H_7)-C_2H_5$, $-(CH_2)_3-CH(C_3H_7)-CH_3$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH=CH-C_2H_5$, $-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH-CH_3$, $-CH=CH-CH=CH_2$, $-C_3H_6-CH=CH_2$, $-C_2H_4-CH=CH-CH_3$, $-CH_2-CH=CH-C_2H_5$, $-CH=CH-C_3H_7$, $-CH_2-CH=CH-CH=CH_2$, $-CH=CH-CH=CH-CH_3$, $-CH=CH-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$, $-CH=CH-C(CH_3)=CH_2$, $-C_2H_4-C(CH_3)=CH_2$, $-CH_2-CH(CH_3)-CH=CH_2$, $-CH(CH_3)-CH_2-CH=CH_2$, $-CH_2-CH=C(CH_3)_2$, $-CH_2-C(CH_3)=CH-CH_3$, $-CH(CH_3)-CH=CH-CH_3$, $-CH=CH-CH(CH_3)_2$, $-CH=C(CH_3)-C_2H_5$, $-C(CH_3)=CH-C_2H_5$, $-C(CH_3)=C(CH_3)_2$, $-C(CH_3)_2-CH=CH_2$, $-CH(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$, $-CH=CH-C(CH_3)=CH_2$, $-C_4H_8-CH=CH_2$, $-C_3H_6-CH=CH-CH_3$, $-C_2H_4-CH=CH-C_2H_5$, $-CH_2-CH=CH-C_3H_7$, $-CH=CH-C_4H_9$, $-C_3H_6-C(CH_3)=CH_2$, $-C_2H_4-CH(CH_3)-CH=CH_2$, $-CH_2-CH(CH_3)-CH_2-CH=CH_2$, $-CH(CH_3)-C_2H_4-CH=CH_2$,

$-C_2H_4-CH=C(CH_3)_2$, $-C_2H_4-C(CH_3)=CH-CH_3$, $-CH_2-CH(CH_3)-CH=CH-CH_3$, $-CH(CH_3)-CH_2-CH=CH-CH_3$, $-CH_2-CH=CH-CH(CH_3)_2$, $-CH_2-CH=C(CH_3)-C_2H_5$, $-CH_2-C(CH_3)=CH-C_2H_5$, $-CH(CH_3)-CH=CH-C_2H_5$, $-CH=CH-CH_2-CH(CH_3)_2$, $-CH=CH-CH(CH_3)-C_2H_5$, $-CH=C(CH_3)-C_3H_7$, $-C(CH_3)=CH-C_3H_7$, $-CH_2-CH(CH_3)-C(CH_3)=CH_2$, $-CH(CH_3)-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH(CH_3)-CH=CH_2$, $-CH_2-C(CH_3)_2-CH=CH_2$, $-C(CH_3)_2-CH_2-CH=CH_2$, $-CH_2-C(CH_3)=C(CH_3)_2$, $-CH(CH_3)-CH=C(CH_3)_2$, $-C(CH_3)_2-CH=CH-CH_3$, $-CH(CH_3)-C(CH_3)=CH-CH_3$, $-CH=C(CH_3)-CH(CH_3)_2$, $-C(CH_3)=CH-CH(CH_3)_2$, $-C(CH_3)=C(CH_3)-C_2H_5$, $-CH=CH-C(CH_3)_3$, $-C(CH_3)_2-C(CH_3)=CH_2$, $-CH(C_2H_5)-C(CH_3)=CH_2$, $-C(CH_3)(C_2H_5)-CH=CH_2$, $-CH(CH_3)-C(C_2H_5)=CH_2$, $-CH_2-C(C_3H_7)=CH_2$, $-CH_2-C(C_2H_5)=CH-CH_3$, $-CH(C_2H_5)-CH=CH-CH_3$, $-C(C_4H_9)=CH_2$, $-C(C_3H_7)=CH-CH_3$, $-C(C_2H_5)=CH-C_2H_5$, $-C(C_2H_5)=C(CH_3)_2$, $-C[C(CH_3)_3]=CH_2$, $-C[CH(CH_3)(C_2H_5)]=CH_2$, $-C[CH_2-CH(CH_3)_2]=CH_2$, $-C_2H_4-CH=CH-CH=CH_2$, $-CH_2-CH=CH-CH_2-CH=CH_2$, $-CH=CH-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH=CH-CH_3$, $-CH=CH-CH_2-CH=CH-CH_3$, $-CH=CH-CH=CH-C_2H_5$, $-CH_2-CH=CH-C(CH_3)=CH_2$, $-CH_2-CH=C(CH_3)-CH=CH_2$, $-CH_2-C(CH_3)=CH-CH=CH_2$, $-CH(CH_3)-CH=CH-CH=CH_2$, $-CH=CH-CH_2-C(CH_3)=CH_2$, $-CH=CH-CH(CH_3)-CH=CH_2$, $-CH=C(CH_3)-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH_2-CH=CH_2$, $-CH=CH-CH=C(CH_3)_2$, $-CH=CH-C(CH_3)=CH-CH_3$, $-CH=C(CH_3)-CH=CH-CH_3$, $-C(CH_3)=CH-CH=CH-CH_3$, $-CH=C(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-C(CH_3)=CH_2$, $-C(CH_3)=C(CH_3)-CH=CH_2$, $-CH=CH-CH=CH-CH=CH_2$, $-C\equiv CH$, $-C\equiv C-CH_3$, $-CH_2-C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-C\equiv C-C_2H_5$, $-C_3H_6-C\equiv CH$, $-C_2H_4-C\equiv C-CH_3$, $-CH_2-C\equiv C-C_2H_5$, $-C\equiv C-C_3H_7$, $-CH(CH_3)-C\equiv CH$, $-CH_2-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C\equiv C-CH_3$, $-C_4H_8-C\equiv CH$, $-C_3H_6-C\equiv C-CH_3$, $-C_2H_4-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-C_3H_7$, $-C\equiv C-C_4H_9$, $-C_2H_4-CH(CH_3)-C\equiv CH$, $-CH_2-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C_2H_4-C\equiv CH$, $-CH_2-CH(CH_3)-C\equiv C-CH_3$, $-CH(CH_3)-CH_2-C\equiv C-CH_3$, $-CH(CH_3)-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-CH(CH_3)_2$, $-C\equiv C-CH(CH_3)-C_2H_5$, $-C\equiv C-CH_2-CH(CH_3)_2$, $-C\equiv C-C(CH_3)_3$, $-CH(C_2H_5)-C\equiv C-CH_3$, $-C(CH_3)_2-C\equiv C-CH_3$, $-CH(C_2H_5)-CH_2-C\equiv CH$, $-CH_2-CH(C_2H_5)-C\equiv CH$, $-C(CH_3)_2-CH_2-C\equiv CH$, $-CH_2-C(CH_3)_2-C\equiv CH$, $-CH(CH_3)-CH(CH_3)-C\equiv CH$, $-CH(C_3H_7)-C\equiv CH$, $-C(CH_3)(C_2H_5)-C\equiv CH$, $-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-C\equiv CH$, $-C\equiv C-C\equiv C-CH_3$, $-CH(C\equiv CH)_2$, $-C_2H_4-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-CH_2-C\equiv CH$, $-C\equiv C-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-C\equiv C-CH_3$, $-C\equiv C-CH_2-C\equiv C-CH_3$,

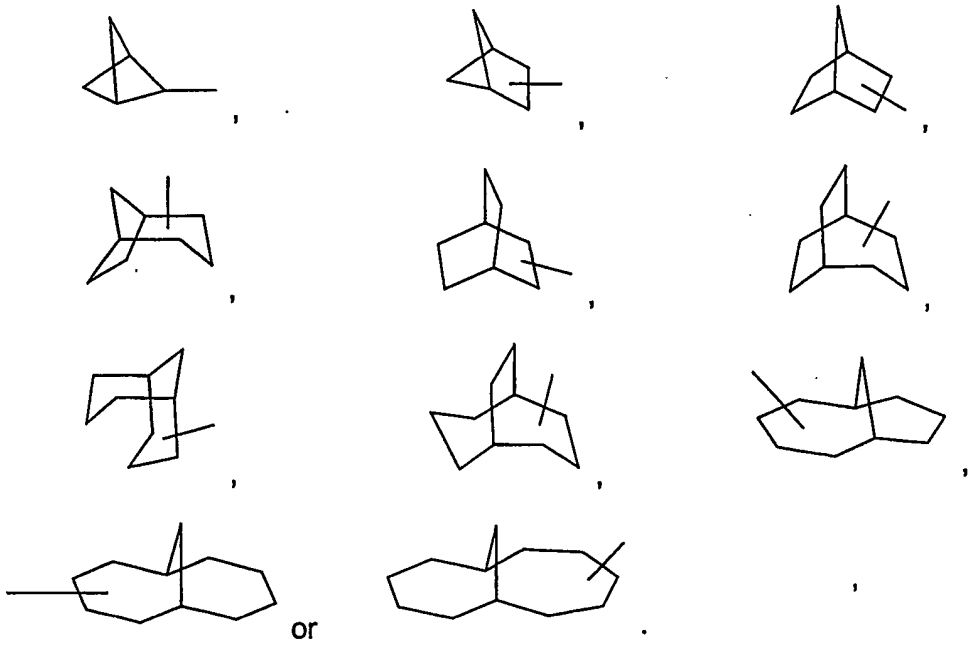
$-C\equiv C-C\equiv C-C_2H_5$, $-C\equiv C-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-C\equiv C-C\equiv CH$,
$-CH(C\equiv CH)-CH_2-C\equiv CH$, $-C(C\equiv CH)_2-CH_3$, $-CH_2-CH(C\equiv CH)_2$,
$-CH(C\equiv CH)-C\equiv C-CH_3$, $-C\equiv C-CH=CH_2$, $-CH=CH-C\equiv CH$,
$-CH_2-C\equiv C-CH=CH_2$, $-CH_2-CH=CH-C\equiv CH$, $-C\equiv C-CH=CH-CH_3$,
$-CH=CH-C\equiv C-CH_3$, $-C\equiv C-CH_2-CH=CH_2$, $-CH=CH-CH_2-C\equiv CH$,
$-C\equiv C-CH_2-C\equiv CH$, $-C(CH_3)=CH-C\equiv CH$, $-CH=C(CH_3)-C\equiv CH$,
$-C\equiv C-C(CH_3)=CH_2$, and $-C\equiv C-C\equiv C-C\equiv CH$.

The term linear or branched C_1–C_6 substituted or unsubstituted alkyl, linear or branched C_1–C_4 substituted or unsubstituted alkyl or linear or branched C_2–C_4 alkenyl is meant to include the respective subgroup out of the above groups.

The term C_3–C_8 cycloalkyl denotes the following cycloalkyls:



The term C_5–C_{12} bicycloalkyl is meant to include the following bicycloalkyls:



The term aryl denotes an aromatic mono- or bicyclic 6 to 10 membered ring system such as phenyl, naphthyl, 3-chlorophenyl, 2,6-dibromophenyl, 2,4,6-tribromophenyl, 4,7-dichloronaphthyl, and preferably phenyl or naphthyl.

The term heterocyclyl is meant to include a 5 to 10 membered mono- or bicyclic ringsystem, containing one to three heteroatoms independently selected from oxygen, sulfur or nitrogen and is preferably selected from the group comprising:
Aziridinyl, azetidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, piperadizinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl or morpholinyl.

The term heterocyclyl further comprises all heteroaryls as defined below, wherein all double bonds of the correspondent heteroaryls are replaced by single bonds.

The term heteroaryl denotes a partially or fully unsaturated 5 to 10 membered mono- or bicyclic ringsystem, containing one to three heteroatoms independently selected from oxygen, sulfur or nitrogen and is preferably selected from the group consisting of:
Pyrrolyl, furanyl, thiophenyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrazinyl, pyrazyl, pyradizinyl, pyradizyl, 3-methylpyridyl, benzothienyl, 4-ethylbenzothienyl, 3,4-diethylfuranyl, pyrrolyl, tetrahydroquinolyl, quinolyl, tetrahydroisoquinolinyl, isoquinolinyl, benzoimidazolyl, benzothiazolyl, benzooxyzolyl, benzo[1,3]dioxolyl, indolyl, benzofuranyl, benzothiophenyl, indazolyl or chrom-2-onyl.

It is to be understood, that the term heteroaryl also comprises partially unsaturated 5 to 10 membered mono- or bicyclic ringsystem, wherein one up to 4 double bonds of the ringsystem are replaced by a single bond and wherein the ringsystem contains at least one double bond.

In a preferred embodiment of the present invention, R^1 in the compounds according to the general formula (I) is selected from –H or linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably from –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl, more preferably from –H or $-CH_3$, and is most preferably –H.

In a further preferred embodiment of the present invention, R^2 in the compounds according to the general formula (I) is selected from –H, $-NH_2$ or linear or

branched substituted or unsubstituted C_1–C_6 alkyl, preferably from –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl, and is more preferably –H.

In yet another preferred embodiment of the present invention, **R^4** in the compounds according to the general formula (I) is selected from –H, $-NH_2$ or linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably from –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl, more preferably from –H or $-CH_3$, and is most preferably –H.

In yet another preferred embodiment of the present invention, **m** in the compounds according to the general formula (I) is selected to be 0, **R^3** is selected from the group comprising:
Substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, more preferably substituted phenyl, and
R^5 is selected from the group consisting of:
Substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, more preferably substituted phenyl, or $-(CH_2)_o$–Y. wherein o is an integer from 0 to 4 and Y represents substituted or unsubstituted heteroaryl, preferably unsubstituted heteroaryl.
In yet another preferred embodiment of the present invention, R^3 and R^5 in the compounds according to the general formula (I) represent phenyl, wherein each phenyl is independently of each other partially or fully substituted with members selected from the group consisting of:
Linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably linear or branched substituted or unsubstituted C_1–C_4 alkyl, more preferably $-CH_3$, linear or branched C_1–C_6 alkoxy, preferably linear or branched C_1–C_4 alkoxy, more preferably $-OCH_3$, $-O-(CH_2)_u$–Phenyl, wherein u is an integer from 0 to 6, preferably from 0 to 4, more preferably from 0 to 2,
$-NR^{20}R^{21}$, wherein R^{20} and R^{21} are independently of each other selected from –H or linear or branched substituted or unsubstituted C_1–C_6 alkyl, more preferably from –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl, and are most preferably –H, $-COOR^{22}$, wherein R^{22} represents linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably linear or branched substituted or unsubstituted C_1–C_4 alkyl, more preferably $-CH_3$, or phenyl is substituted with heteroaryl selected from benzoimidazolyl, benzothiazolyl or benzoxazolyl,
and wherein each phenyl is preferably mono-, di- or trisubstituted, more preferably mono- or disubstituted.

In yet another preferred embodiment of the present invention, R^5 in the compounds according to the general formula (I) represents $-(CH_2)_o-Y$, wherein o is selected to be 2 and wherein Y represents unsubstituted pyridinyl, preferably unsubstituted 4-pyridinyl.

In another preferred embodiment of the present invention, m in the compounds according to the general formula (I) is selected to be **1**.

In yet another preferred embodiment of the present invention, R^3 in the compounds according to the general formula (I) is selected from the group comprising:
–Cl, –Br, –I, preferably –Cl or –Br, more preferably –Cl,
substituted or unsubstituted aryl, substituted or unsubstituted –CH=CH–aryl, preferably substituted or unsubstituted –CH=CH–phenyl, more preferably unsubstituted –CH=CH–phenyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, preferably substituted heterocyclyl, substituted or unsubstituted C_3–C_8 cycloalkyl, substituted or unsubstituted W-heterocyclyl, wherein W is selected to be –NH, preferably substituted –NH-heterocyclyl or R^3 represents $-NH-(CH_2)_n-X$, wherein n is an integer from 0 to 4, preferably from 0 to 2, and X is selected from –OH, $-NH_2$ or substituted or unsubstituted C_3–C_8 cycloalkyl, preferably unsubstituted cycloalkyl, more preferably unsubstituted cyclohexyl.

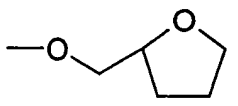
In yet another preferred embodiment of the present invention, R^3 in the compounds according to the general formula (I) represents partially or fully substituted **heterocyclyl,** wherein the heterocyclyl is selected from the group consisting of: Pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, preferably substituted piperazinyl, wherein piperazinyl is N-substituted with linear or branched substituted or unsubstituted C_1–C_4 alkyl, preferably $-CH_3$.

In yet another preferred embodiment of the present invention, R^3 in the compounds according to the present invention represents substituted or unsubstituted **heteroaryl**, wherein the heteroaryl is selected from the group comprising:
Pyridinyl, pyridyl, pyridazinyl, pyrimidinyl, imidazolyl, pyrimidyl, pyrazinyl, pyrazyl, thiophenyl, thienyl, furanyl or pyrrolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, pyrazyl, pyradizinyl, pyradizyl, 3-methylpyridyl, benzothienyl, 4-ethylbenzothienyl, 3,4-diethylfuranyl, pyrrolyl, tetrahydroquinolyl, quinolyl, tetrahydroisoquinolinyl,

isoquinolinyl, benzoimidazolyl, benzothiazolyl, benzooxyzolyl, benzo[1,3]dioxolyl, indolyl, benzofuranyl, benzothiophenyl, indazolyl or chrom-2-onyl and preferably pyridinyl, pyridyl, pyrimidinyl, pyrimidyl, thiophenyl or furanyl, more preferably 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, pyrimidinyl, 2-thiophenyl or 2-furanyl, and wherein the substituted heteroaryl is selected from furanyl, thiophenyl or pyridinyl, preferably 3-pyridinyl or 2-thiophenyl, partially or fully substituted with linear or branched C_1-C_4 alkoxy, preferably with $-OCH_3$, or with $-CO-CH_3$, and wherein the pyridinyl or thiophenyl are preferably monosubstituted.

In another preferred embodiment of the present invention, R^3 in the compounds according to the present invention represents substituted or unsubstituted phenyl, preferably substituted phenyl, wherein within this embodiment phenyl is partially or fully substituted with members of the group consisting of:
–F, –Cl, –Br, –I, preferably –F or –Cl, –CN, $-NO_2$,
linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably linear or branched substituted or unsubstituted C_1–C_4 alkyl, linear or branched C_2–C_6 alkenyl, preferably linear or branched C_2–C_4 alkenyl, substituted or unsubstituted phenyl, preferably unsubstituted phenyl,
linear or branched C_1–C_6 alkoxy, preferably linear or branched C_1–C_4 alkoxy,
$-O-(CH_2)_v-R$, wherein v is an integer from 0 to 6, preferably from 0 to 4 and R is selected from the group consisting of:
Phenyl, –O–phenyl, linear or branched substituted or unsubstituted C_1–C_4 haloalkyl, heterocyclyl, or $-NR^{23}R^{24}$, wherein R^{23} and R^{24} are independently of each other selected from –H or linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably from –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl,
linear or branched C_1–C_6 haloalkyl, preferably linear or branched C_1–C_4 haloalkyl,
linear or branched C_1–C_6 thioalkyl, preferably linear or branched C_1–C_4 thioalkyl,
$-(CH_2)_w-Q$, wherein w is selected to be an integer from 0 to 6, preferably from 0 to 4 and Q is selected from heterocyclyl, –OH, $-NR^{25}R^{26}$, wherein R^{25} and R^{26} are independently of each other selected from –H, linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl, or $-(CH_2)_y-O-CH_3$, wherein y is selected to be an integer from 0 to 6, preferably from 0 to 4, or Q represents linear or branched C_1–C_6 alkoxy, preferably linear or branched C_1–C_4 alkoxy,
$-(CH_2)_y-COR^{27}$, wherein y is an integer from 0 to 6, preferably from 0 to 4, and R^{27} is selected from the group comprising:

–H, linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably linear or branched substituted or unsubstituted C_1–C_4 alkyl, $-OR^{28}$, wherein R^{28} is selected from –H or linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably linear or branched substituted or unsubstituted C_1–C_4 alkyl, or R^{28} is selected from $-NR^{29}R^{30}$, wherein R^{29} and R^{30} are independently of each other selected from –H, linear or branched substituted or unsubstituted C_1–C_6 alkyl or C_3–C_8 cycloalkyl, preferably from –H, linear or branched substituted or unsubstituted C_1–C_4 alkyl or C_4–C_6 cycloalkyl,
–CH=CH–COOH, $-CH=CH-COOCH_3$ or $-NH-T-R^{31}$, wherein T is selected from –CO– or $-SO_2-$ and R^{31} represents linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably linear or branched C_1–C_4 alkyl, and
wherein phenyl is mono-, di- or trisubsituted, preferably mono- or disubstituted, and wherein within this embodiment, it is especially preferred, that phenyl is substituted with members of the group consisting of:
–F, –Cl, –CN, $-C_2H_5$, $-CH(CH_3)_2$, $-CH=CH_2$, $-OCH_3$, $-OC_2H_5$, $-OCH(CH_3)_2$, –O–Phenyl, $-O-CH_2$–Phenyl, $-O-(CH_2)_2-O$–Phenyl, $-O-(CH_2)_2-N(CH_3)_2$, $-O-(CH_2)_3-N(CH_3)_2$, $-O-(CH_2)_3-NH_2$, $-OCF_3$, –OH, $-CH_2-OH$, $-CH_2-OCH_3$, $-SCH_3$, $-NH_2$, $-N(CH_3)_2$, $-CH_2-NH_2$, $-CH_2-N(CH_3)_2$, $-CH=CH-COOH$, $-CH=CH-COOCH_3$, –COOH, $-(CH_2)_2-COOH$, $-COOCH_3$, $-CF_3$, Phenyl, –C(O)–H, $-C(O)-CH_3$, $-C(O)-NH_2$, $-C(O)-NHCH(CH_3)_2$, $-NH-CO-CH_3$, $-NH-SO_2-CH_3$, $-CH_2-N(CH_3)-(CH_2)_2-O-CH_3$,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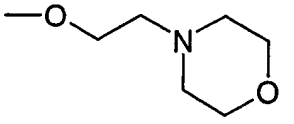
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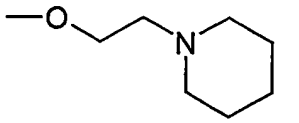
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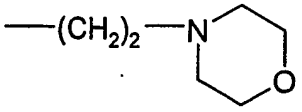
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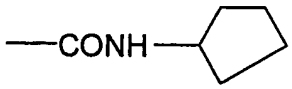
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preferably phenyl is substituted with $-OCH_3$, $-O-CH_2$–Phenyl, –OH, $-OCH(CH_3)_2$ or $-NH_2$.

In a further preferred embodiment of the present invention, R^5 in the compounds according to the general formula (I) is selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl.

In yet another preferred embodiment of the present invention, R^5 in the compounds according to the general formula (I) represents substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, more preferably unsubstituted phenyl.

It is especially preferred, if R^5 in the compounds according to the general formula (I) represents a substituted phenyl, that phenyl is partially or fully substituted with linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably with linear or branched substituted or unsubstituted C_1–C_4 alkyl, more preferably with $-CH_3$ or phenyl is partially or fully substituted with $-O-(CH_2)_u-$Phenyl, wherein u is an integer from 0 to 6, preferably from 0 to 4, more preferably from 0 to 2, and is most preferably 1, and wherein phenyl is preferably monosubstituted.

In a further preferred embodiment, **L** in the compounds according to the general formula (I) is selected from the group comprising:

$-NR^{14}-SO_2-$,

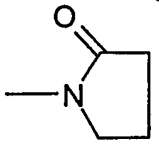
wherein R^{14} is selected from –H, linear or branched substituted or unsubstituted C_1–C_4 alkyl, $-SO_2-R^{15}-$, $-R^{15}-SO_2-$,

wherein R^{15} is selected from linear or branched substituted or unsubstituted C_1–C_4 alkylen,

or R^{14} represents $-(CH_2)_r-COOR^{16}$, wherein r is an integer from 0 to 4 and R^{16} is selected from –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl,

$-NR^{17}-CO-$,

wherein R^{17} is selected from –H, linear or branched substituted or unsubstituted C_1–C_4 alkyl, or a $-(CH_2)_s-$group, wherein s is an integer from 1 to 3, preferably s is selected to be 1, and wherein if R^6 represents a $-(CH_2)_q-$group, wherein q is an integer from 1 to 3, preferably q is selected to be 2 and R^{17} represents a methylene chain $-(CH_2)_s-$group, R^6 and R^{17} may form together a 5 to 8 membered ring system, preferably R^6 and R^{17} form together a 5 membered ring system



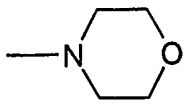
,

$-SO_2-NR^{18}-$,

wherein R^{18} is selected from –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl,

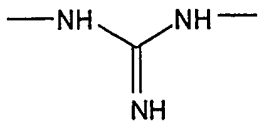
$-CO-NR^{19}-$,

wherein R^{19} is selected from –H, linear or branched substituted or unsubstituted C_1–C_4 alkyl, or a $-(CH_2)_t-A-$ group, wherein t is an integer from 1 to 3 and A is selected from N or O, and wherein if R^6 represents a $-(CH_2)_q-$group wherein q is an integer from 1 to 3, preferably q is selected to be 2 and R^{19} represents a $-(CH_2)_t-A-$ group, wherein t is selected to be 2 and A represents O, R^6 and R^{19} may form together a 6-membered ring system



,

$-NH-CO-NH-$, $-SO_2-$ or



;

and wherein within this embodiment, it is especially preferred, that if R^5 represents phenyl, L is preferably in meta- or para-position of the phenyl.

In yet another preferred embodiment of the present invention, L in the compounds according to the general formula (I) is selected from the group consisting of:

$-NR^{14}-SO_2-$,

wherein R^{14} is selected from –H, $-(CH_2)_2-CH_3$, $-SO_2-R^{15}$ or $-R^{15}-SO_2-$, wherein R^{15} represents linear or branched substituted or unsubstituted C_1–C_4 alkylen or $-(CH_2)_2-CH_3$, or $-(CH_2)_r-COOR^{16}$, wherein r is selected to be an integer from 0 to 2, and is preferably 1, and R^{16} represents $-CH_3$,

$-NR^{17}-CO-$, $-SO_2-NR^{18}-$, $-CO-NR^{19}-$,

wherein R^{17}, R^{18} and R^{19} represent –H, $-NH-CO-NH-$ or $-SO_2-$, wherein within this embodiment it is especially preferred, that L is selected from $-NH-SO_2-$, $-NH-CO-$, $-CO-NH-$, $-SO_2-NH-$ $-NH-CO-NH-$ or $-SO_2-$.

In yet another preferred embodiment of the present invention, **R^6** in the compounds according to the general formula (I) is selected from the group comprising:

–H, linear or branched substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or

unsubstituted heterocyclyl, substituted pyrrolidinyl, substituted or unsubstituted C_3–C_8 cycloalkyl, disubstituted cyclohexyl, cyclopentyl, substituted or unsubstituted C_5–C_{12} bicycloalkyl, substituted or unsubstituted adamantyl, or $-(CH_2)_p-Z$, wherein p is an integer from 0 to 4 and Z is selected from the group comprising:
substituted or unsubstituted aryl, preferably unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, $-N(R^7R^8)$, wherein R^7 and R^8 represent independently from each other –H, or linear or branched C_1–C_6 alkyl, or Z represents $-(CR^9R^{10}R^{11})$, wherein R^9, R^{10} and R^{11} are independently of each other selected from the group consisting of: –H, linear or branched substituted or unsubstituted C_1–C_4 alkyl, substituted or unsubstituted aryl or $-N(R^{12}R^{13})$, wherein R^{12} and R^{13} represent independently of each other –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl, and wherein if Z is selected from substituted or unsubstituted aryl, preferably unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, p can not be selected to be 0.

In yet another preferred embodiment of the present invention, **R^6** in the compounds according to the general formula (I) is selected from the group consisting of:
–H, linear or branched substituted or unsubstituted C_1–C_6 alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted C_3–C_8 cycloalkyl, unsubstituted C_5–C_{12} bicycloalkyl, preferably unsubstituted bicyclo[2.2.1] heptanyl, unsubstituted adamantyl or $-(CH_2)_p-Z$, wherein p is an integer from 0 to 2 and Z is selected from the group comprising:
substituted or unsubstituted phenyl, substituted or unsubstituted heterocyclyl, $-N(R^7R^8)$, wherein R^7 and R^8 represent independently from each other –H, or linear or branched substituted or unsubstituted C_1–C_4 alkyl, or Z represents $-(CR^9R^{10}R^{11})$, wherein R^9, R^{10} and R^{11} are independently of each other selected from the group consisting of: –H, linear or branched substituted or unsubstituted C_1–C_6 alkyl, unsubstituted aryl or $-N(R^{12}R^{13})$, wherein R^{12} and R^{13} represent independently of each other –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl.

In yet another preferred embodiment according to the present invention, R^6 in the compounds according to the general formula (I) represents –H or linear or branched **C_1–C_6 alkyl**, preferably –H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C(CH_3)_3$ or $-CH_2-C(CH_3)_3$, more preferably –H, $-CH_3$ or $-C(CH_3)_3$.

In yet another preferred embodiment according to the present invention, R^6 in the compounds according to the general formula (I) represents substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl or naphtyl, wherein if R^6 represents substituted naphthyl, napthyl is partially or fully substituted with –OH or linear or branched C_1–C_4 alkoxy, preferably –OH and wherein napthyl is preferably monosubstituted,
or wherein if R^6 represents substituted phenyl, phenyl is partially or fully substituted with members of the group comprising:
Phenyl, linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably linear or branched substituted or unsubstituted C_1–C_4 alkyl, more preferably $-CH_3$, $-C_3H_7$, $-CH(CH_3)_2$ or $-C(CH_3)_3$, substituted or unsubstituted heterocyclyl, preferably unsubstituted morpholinyl or N-substituted piperazinyl, wherein N-substituted piperazinyl is substituted with linear or branched C_1–C_4 alkyl, preferably with $-CH_3$, or phenyl is partially or fully substituted with –OH or $-N(R^{32}R^{33})$, wherein R^{32} and R^{33} represent independently of each other –H or linear or branched C_1–C_4 alkyl, preferably –H or $-CH_3$, more preferably –H.

In yet another preferred embodiment according to the present invention, R^6 in the compounds according to the general formula (I) represents substituted or unsubstituted heteroaryl, wherein the **heteroaryl** is selected from the group comprising:
Pyrrolyl, thiophenyl, furanyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothioazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyradizinyl, tetrahydroquinolinyl, quinolinyl, isoquinolinyl, benzoimidazolyl, benzothiazolyl, benzooxazolyl, benzo[1,3]dioxolyl, indolyl, benzofuranyl, benzothiophenyl, indazolyl or chrom-2-onyl,
preferably R^6 is selected from the group consisting of:
imidazolyl, wherein preferably one N-atom of the imidazolyl, is substituted with linear or branched substituted or unsubstituted C_1–C_4 alkyl, more preferably with $-CH_3$,
pyridinyl, preferably 4-pyridinyl, tetrahydroquinolinyl, quinolinyl, benzoimidazolyl, benzothiazolyl, benzo[1,3]dioxolyl, indolyl, indazolyl or chromen-2-onyl.

In yet another preferred embodiment according to the present invention, R^6 in the compounds according to the general formula (I) represents substituted or unsubstituted **heterocyclyl**, wherein heterocyclyl is selected from the group comprising:
Aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl,

preferably R^6 is selected from azetidinyl, pyrrolidinyl, preferably 2-pyrrolidinyl or 2-piperidinyl, 3-piperidinyl or 4-piperidinyl, preferably 2-piperidinyl.

It is especially preferred within the embodiment described above, that R^6 in the compounds according to the general formula (I) represents partially or fully substituted heterocyclyl, preferably partially or fully substituted piperidinyl, more preferably N-substituted piperidinyl, substituted with linear or branched substituted or unsubstituted C_1–C_4 alkyl, preferably $-CH_3$, or $-N-COOR^{34}$, wherein R^{34} represents –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl, preferably $-(CCH_3)_3$.

In yet another preferred embodiment of the present invention, R^6 in the compounds according to the general formula (I) represents substituted or unsubstituted C_3–C_8 cycloalkyl, preferably substituted or unsubstituted cyclopentyl or cyclohexyl, and wherein cyclopentyl or cyclohexyl are partially or fully substituted with linear or branched substituted or unsubstituted C_1–C_6 alkyl, –OH, $-NH_2$ or $-NH-COOR^{35}$, wherein R^{35} represents –H or linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably linear or branched C_1–C_4 alkyl, more preferably $-C(CH_3)_3$, and wherein cyclopentyl or cyclohexyl are preferably substituted with $-NH_2$, and wherein cyclopentyl or cyclohexyl are preferably mono-, di- or trisubstituted, more preferably monosubstituted.

In yet another preferred embodiment of the present invention, R^6 in the compounds according to the general formula (I) represents $-(CH_2)_p-Z$, wherein p is selected to be 1 or 2 and Z is selected from the group comprising:

Substituted or unsubstituted phenyl, wherein in case phenyl is substituted, it is substituted with linear or branched substituted or unsubstituted C_1–C_4 alkyl, preferably $-CH_3$,

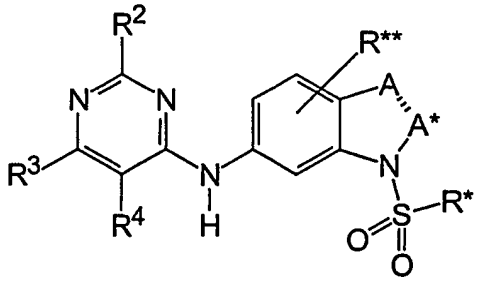
substituted or unsubstituted heterocyclyl, preferably substituted or unsubstiuted piperidinyl, more preferably N-substituted or unsubstituted 2-piperidinyl, wherein in case 2-piperidinyl is N-substituted, it is substituted with $-COOR^{36}$, wherein R^{36} represents linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably linear or branched C_1–C_4 alkyl, more preferably $-C(CH_3)_3$, or Z represents $-N(R^7R^8)$, wherein R^7 and R^8 represent independently of each other –H, or linear or branched C_1–C_4 alkyl, preferably –H, $-CH_3$ or $-C_2H_5$,

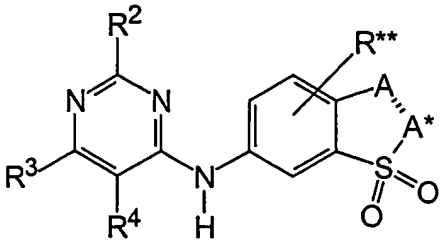
or R^6 represents $-(CH_2)_p-Z$, wherein p is selected to be an integer from 0 to 2 and Z is selected to be $-(CR^9R^{10}R^{11})$, wherein R^9, R^{10} and R^{11} are independently of each other selected from the group consisting of:

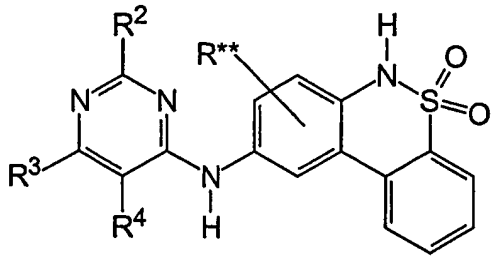
–H, linear or branched substituted or unsubstituted C_1–C_5 alkyl, preferably –CH_3, –$CH(CH_3)_2$, or–$CH(CH_3)$–C_2H_5, substituted or unsubstituted aryl, or –$N(R^{12}R^{13})$, wherein R^{12} and R^{13} represent independently of each other –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl, preferably –H or –CH_3.

In a further preferred embodiment of the present invention, m in the compounds according to the general formula (I) is selected to be 1, R^1, R^2 and R^4 represent –H, R^3 represents monosubstituted phenyl, R^5 represents monosubstituted or unsubstituted phenyl, L is selected from the group comprising:
–NH–CO–, –NH–SO_2–, –SO_2–NH–, –CO–NH– or –SO_2– , and
R^6 is selected from the group consisting of:
–H, linear or branched substituted or unsubstituted C_1–C_4 alkyl, monosubstituted phenyl, substituted or unsubstituted heterocyclyl, wherein heterocyclyl is preferably selected from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl, substituted or unsubstituted heteroaryl, wherein heteroaryl is selected from imidazolyl, pyridinyl, tetrahydroquinolinyl, quinolinyl, benzoimidazolyl, benzothiazolyl, benzo[1,3]dioxolyl, indolyl, indazolyl or chromen-2-only or R^6 represents substituted or unsubstituted C_3–C_8 cycloalkyl.

Especially preferred compounds of general formula (I) are represented by the following subformula







wherein A-A* represents –CH_2–CH_2–, –CH=CH–, –NH–CH_2–, –CH_2–NH–, –N=CH–, –CH=N–, –N=N–,

R* is a substituted or unsubstituted aryl, linear or branched substituted or unsubstituted alkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted cycloalkyl, C_2–C_6 alkenyl or C_2–C_6 alkinyl,

R** represents hydrogen, linear or branched substituted or unsubstituted alkyl or an substitutent selected form Sub.

R^2, R^3, and R^4 have the meanings as defined above.

Preferably R* is substituted or unsubstituted C_1–C_6 alkyl and most preferably methyl. R^3 represents preferably phenyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl and especially an alkoxy substituted phenyl.

In yet another preferred embodiment of the present invention, compounds according to the general formula (I) are chiral compounds. It is to be understood, that chiral compounds according to the present invention represent a racemate, or a S or a R enantiomer or a mixture of isomers, respectively.

As used herein, the term "substituent", or "Sub" or the possibility that one residue may be further substituted with another group refers to the following list of substituents which may be present independently of each other:

–H, –OH, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, –O–cyclo-C_3H_5, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, $-OC_4H_9$, –OPh, $-OCH_2$–Ph, $-OCPh_3$, –SH, $-SCH_3$, $-SC_2H_5$, $-SC_3H_7$, –S–cyclo-C_3H_5, $-SCH(CH_3)_2$, $-SC(CH_3)_3$, $-NO_2$, –F, –Cl, –Br, –I, $-N_3$, –CN, –OCN, –NCO, –SCN, –NCS, –CHO, $-COCH_3$, $-COC_2H_5$, $-COC_3H_7$, –CO–cyclo-C_3H_5, $-COCH(CH_3)_2$, $-COC(CH_3)_3$, –COOH, –COCN, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, –COO–cyclo-C_3H_5, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, –OOC–CH_3, –OOC–C_2H_5, –OOC–C_3H_7, –OOC–cyclo-C_3H_5, –OOC–$CH(CH_3)_2$, –OOC–$C(CH_3)_3$, $-CONH_2$, $-CONHCH_3$, $-CONHC_2H_5$, $-CONHC_3H_7$, –CONH–cyclo-C_3H_5, $-CONH[CH(CH_3)_2]$, $-CONH[C(CH_3)_3]$, $-CON(CH_3)_2$, $-CON(C_2H_5)_2$, $-CON(C_3H_7)_2$, $-CON(\text{cyclo-}C_3H_5)_2$, $-CON[CH(CH_3)_2]_2$, $-CON[C(CH_3)_3]_2$, $-NH_2$, $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, –NH–cyclo-C_3H_5, $-NHCH(CH_3)_2$, $-NHC(CH_3)_3$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N(C_3H_7)_2$, $-N(\text{cyclo-}C_3H_5)_2$, $-N[CH(CH_3)_2]_2$, $-N[C(CH_3)_3]_2$, $-SOCH_3$, $-SOC_2H_5$, $-SOC_3H_7$, –SO–cyclo-C_3H_5, $-SOCH(CH_3)_2$, $-SOC(CH_3)_3$, $-SO_2CH_3$, $-SO_2C_2H_5$, $-SO_2C_3H_7$, $-SO_2$–cyclo-C_3H_5, $-SO_2CH(CH_3)_2$, $-SO_2C(CH_3)_3$, $-SO_3H$, $-SO_3CH_3$, $-SO_3C_2H_5$, $-SO_3C_3H_7$, $-SO_3$–cyclo-C_3H_5, $-SO_3CH(CH_3)_2$, $-SO_3C(CH_3)_3$, $-OCF_3$, $-OC_2F_5$, –O–$COOCH_3$, –O–$COOC_2H_5$, –O–$COOC_3H_7$, –O–COO–cyclo-C_3H_5, –O–$COOCH(CH_3)_2$, –O–$COOC(CH_3)_3$,

$-NH-CO-NH_2$, $-NH-CO-NHCH_3$, $-NH-CO-NHC_2H_5$, $-NH-CO-NHC_3H_7$, $-NH-CO-NH$-cyclo-C_3H_5, $-NH-CO-NH[CH(CH_3)_2]$, $-NH-CO-NH[C(CH_3)_3]$, $-NH-CO-N(CH_3)_2$, $-NH-CO-N(C_2H_5)_2$, $-NH-CO-N(C_3H_7)_2$, $-NH-CO-N$(cyclo-$C_3H_5)_2$, $-NH-CO-N[CH(CH_3)_2]_2$, $-NH-CO-N[C(CH_3)_3]_2$, $-NH-CS-NH_2$, $-NH-CS-NHCH_3$, $-NH-CS-NHC_2H_5$, $-NH-CS-NHC_3H_7$, $-NH-CS-NH$-cyclo-C_3H_5, $-NH-CS-NH[CH(CH_3)_2]$, $-NH-CS-NH[C(CH_3)_3]$, $-NH-CS-N(CH_3)_2$, $-NH-CS-N(C_2H_5)_2$, $-NH-CS-N(C_3H_7)_2$, $-NH-CS-N$(cyclo-$C_3H_5)_2$, $-NH-CS-N[CH(CH_3)_2]_2$, $-NH-CS-N[C(CH_3)_3]_2$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHCH_3$, $-NH-C(=NH)-NHC_2H_5$, $-NH-C(=NH)-NHC_3H_7$, $-NH-C(=NH)-NH$-cyclo-C_3H_5, $-NH-C(=NH)-NH[CH(CH_3)_2]$, $-NH-C(=NH)-NH[C(CH_3)_3]$, $-NH-C(=NH)-N(CH_3)_2$, $-NH-C(=NH)-N(C_2H_5)_2$, $-NH-C(=NH)-N(C_3H_7)_2$, $-NH-C(=NH)-N$(cyclo-$C_3H_5)_2$, $-NH-C(=NH)-N[CH(CH_3)_2]_2$, $-NH-C(=NH)-N[C(CH_3)_3]_2$, $-O-CO-NH_2$, $-O-CO-NHCH_3$, $-O-CO-NHC_2H_5$, $-O-CO-NHC_3H_7$, $-O-CO-NH$-cyclo-C_3H_5, $-O-CO-NH[CH(CH_3)_2]$, $-O-CO-NH[C(CH_3)_3]$, $-O-CO-N(CH_3)_2$, $-O-CO-N(C_2H_5)_2$, $-O-CO-N(C_3H_7)_2$, $-O-CO-N$(cyclo-$C_3H_5)_2$, $-O-CO-N[CH(CH_3)_2]_2$, $-O-CO-N[C(CH_3)_3]_2$, $-O-CO-OCH_3$, $-O-CO-OC_2H_5$, $-O-CO-OC_3H_7$, $-O-CO-O$-cyclo-C_3H_5, $-O-CO-OCH(CH_3)_2$, $-O-CO-OC(CH_3)_3$, $-CH_2F$ $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, $-CH_2Br$ $-CHBr_2$, $-CBr_3$, $-CH_2I$ $-CHI_2$, $-Cl_3$, $-CH_2-CH_2F$ $-CH_2-CHF_2$, $-CH_2-CF_3$, $-CH_2-CH_2Cl$, $-CH_2-CHCl_2$, $-CH_2-CCl_3$, $-CH_2-CH_2Br$ $-CH_2-CHBr_2$, $-CH_2-CBr_3$, $-CH_2-CH_2I$ $-CH_2-CHI_2$, $-CH_2-Cl_3$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, -cyclo-C_3H_5, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, -Ph, $-CH_2-Ph$, $-CPh_3$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C_2H_4-CH=CH_2$, $-CH=C(CH_3)_2$, $-C\equiv CH$, $-C\equiv C-CH_3$, $-CH_2-C\equiv CH$.

In yet another preferred embodiment of the present invention, the compound according to the general formula (I) is selected from the group of compounds depicted in **Table 2**.

In a further aspect of the present invention, the novel compounds according to the general formula (I) are used as pharmaceutically active agent.

Further aspects of the present invention relate to the use of the compounds of general formula (I) for the preparation of a pharmaceutical composition useful for prophylaxis and/or treatment of infectious diseases including opportunistic diseases, prion diseases, immunological diseases, autoimmune diseases, bipolar and clinical disorders, cardiovascular diseases, cell proliferative diseases,

diabetes, inflammation, transplant rejections, erectile dysfunction, neurodegenerative diseases, and stroke.

Infectious diseases including opportunistic infections

In yet another aspect of the present invention, the compounds according to the general formula (I) are for the preparation of a pharmaceutical composition for the prophylaxis and/or treatment of infectious diseases, including opportunistic diseases and opportunistic infections. The term infectious diseases comprises infections caused by viruses, bacteria, prions, fungi, and/or parasites.

Especially, virally induced infectious diseases, including opportunistic diseases are addressed. In a preferred embodiment of this aspect, the virally induced infectious diseases, including opportunistic diseases, are caused by retroviruses, human endogenous retroviruses (HERVs), hepadnaviruses, herpesviruses, flaviviridae, and/or adenoviruses. Preferably, the retroviruses are selected from lentiviruses or oncoretroviruses, wherein the lentivirus is preferably selected from the group comprising: HIV-1, HIV-2, feline immunodeficiency virus (FIV), bovine immunodeficiency virus (BIV), sivian immunodeficiency viruses (SIVs), chimeras of HIV and SIV (SHIV), caprine arthritis encephalitis virus (CAEV), visna/maedi virus (VMV) or equine infectious anemia virus (EIAV), preferably HIV-1 and HIV-2, and the oncoretrovirus is preferably selected from HTLV-I, HTLV-II or bovine leukemia virus (BLV), preferably HTLV-I and HTLV-II.

The hepadnavirus is preferably selected from HBV, ground squirrel hepatitis virus (GSHV) or woodchuck hepatitis virus (WHV), preferably HBV, the herpesvirus is selected from the group comprising: Herpes simplex virus I (HSV I), herpes simplex virus II (HSV II), Epstein-Barr virus (EBV), varicella zoster virus (VZV), human cytomegalovirus (HCMV) or human herpesvirus 8 (HHV-8), preferably HCMV, and the flaviviridae is selected from HCV, West nile or Yellow Fever.

It is to be understood, that all the viruses mentioned above, also comprise drug resistant virus strains.

Examples of infective diseases are AIDS, Alveolar Hydatid Disease (AHD, Echinococcosis), Amebiasis (Entamoeba histolytica Infection), Angiostrongylus Infection, Anisakiasis, Anthrax, Babesiosis (Babesia Infection), Balantidium Infection (Balantidiasis), Baylisascaris Infection (Raccoon Roundworm), Bilharzia (Schistosomiasis), Blastocystis hominis Infection (Blastomycosis), Boreliosis, Botulism, Brainerd Diarrhea, Brucellosis, BSE (Bovine Spongiform Encephalopathy), Candidiasis, Capillariasis (Capillaria Infection), CFS (Chronic

Fatigue Syndrome), Chagas Disease (American Trypanosomiasis), Chickenpox (Varicella-Zoster virus), Chlamydia pneumoniae Infection, Cholera, Chronic Fatigue Syndrome, CJD (Creutzfeldt-Jakob Disease), Clonorchiasis (Clonorchis Infection), CLM (Cutaneous Larva Migrans, Hookworm Infection), Coccidioidomycosis, Conjunctivitis, Coxsackievirus A16 (Hand, Foot and Mouth Disease), Cryptococcosis, Cryptosporidium Infection (Cryptosporidiosis), Culex mosquito (Vector of West Nile Virus), Cutaneous Larva Migrans (CLM), Cyclosporiasis (Cyclospora Infection), Cysticercosis (Neurocysticercosis), Cytomegalovirus Infection, Dengue / Dengue Fever, Dipylidium Infection (Dog and Cat Flea Tapeworm), Ebola Virus Hemorrhagic Fever, Echinococcosis (Alveolar Hydatid Disease), Encephalitis, Entomoeba coli Infection, Entomoeba dispar Infection, Entomoeba hartmanni Infection, Entomoeba histolytica Infection (Amebiasis), Entomoeba polecki Infection, Enterobiasis (Pinworm Infection), Enterovirus Infection (Non-Polio), Epstein-Barr Virus Infection, Escherichia coli Infection, Foodborne Infection, Foot and mouth Disease, Fungal Dermatitis, Gastroenteritis, Group A streptococcal Disease, Group B streptococcal Disease, Hansen's Disease (Leprosy), Hantavirus Pulmonary Syndrome, Head Lice Infestation (Pediculosis), Helicobacter pylori Infection, Hematologic Disease, Hendra Virus Infection, Hepatitis (HCV, HBV), Herpes Zoster (Shingles), HIV Infection, Human Ehrlichiosis, Human Parainfluenza Virus Infection, Influenza, Isosporiasis (Isospora Infection), Lassa Fever, Leishmaniasis, Kala-azar (Kala-azar, Leishmania Infection), Leprosy, Lice (Body lice, Head lice, Pubic lice), Lyme Disease, Malaria, Marburg Hemorrhagic Fever, Measles, Meningitis, Mosquito-borne Diseases, Mycobacterium avium Complex (MAC) Infection, Naegleria Infection, Nosocomial Infections, Nonpathogenic Intestinal Amebae Infection, Onchocerciasis (River Blindness), Opisthorciasis (Opisthorcis Infection), Parvovirus Infection, Plague, PCP (Pneumocystis carinii Pneumonia), Polio, Q Fever, Rabies, Respiratory Syncytial Virus (RSV) Infection, Rheumatic Fever, Rift Valley Fever, River Blindness (Onchocerciasis), Rotavirus Infection, Roundworms Infection, Salmonellosis, Salmonella Enteritidis, Scabies, Shigellosis, Shingles, Sleeping Sickness, Smallpox, Streptococcal Infection, Tapeworm Infection (Taenia Infection), Tetanus, Toxic Shock Syndrome, Tuberculosis, Ulcers (Peptic Ulcer Disease), Valley Fever, Vibrio parahaemolyticus Infection, Vibrio vulnificus Infection, Viral Hemorrhagic Fever, Warts, Waterborne infectious Diseases, West Nile Virus Infection (West Nile Encephalitis), Whooping Cough, Yellow Fever.

Bacterial infections

As described above, the compounds according to the general formula (I) are also useful for the preparation of a pharmaceutical composition for prophylaxis and / or treatment of bacterially induced infectious diseases, including opportunistic diseases and opportunistic infections, wherein the bacterially induced infectious diseases, including opportunistic diseases, are selected from tuberculosis, leprosy or mycobacteria-induced meningitis. One advantage of the inventive compounds disclosed herein is there use against drug resistant bacteria strains.

Prion diseases

Another aspect of the present invention is directed to the use of at least one compound of the general formula (I) and/or pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of prion diseases.

Prions are infectious agents, which do not have a nucleic acid genome. It seems that a protein alone is the infectious agent. A prion has been defined as "small proteinaceous infectious particle, which resists inactivation, by procedures that modify nucleic acids". The discovery that proteins alone can transmit an infectious disease has come as a considerable surprise to the scientific community. Prion diseases are often called "transmissible spongiform encephalopathies", because of the post mortem appearance of the brain with large vacuoles in the cortex and cerebellum. Probably most mammalian species develop these diseases. Prion diseases are a group of neurodegenerative disorders of humans and animals and the prion diseases can manifest as sporadic, genetic or infectious disorders. Examples for prion diseases acquired by exogenous infection are the Bovine spongiform encephalitis (BSE) of cattle and the new variant of Creutzfeld-Jakob disease (vCJD) caused by BSE as well as scrapie of animals. Examples of human prion diseases include kuru, sporadic Creutzfeldt-Jakob disease (sCJD), familial CJD (fCJD), iatrogenic CJD (iCJD), Gerstmann-Sträussler-Scheinker (GSS) disease, fatal familial insomnia (FFI), and especially the new variant CJD (nvCJD or vCJD).

The name "prion" is used to describe the causative agents, which underlie the transmissible spongiform encephalopathies. A prion is proposed to be a novel infectious particle that differs from viruses and viroids. It is composed solely of one unique protein that resists most inactivation procedures such as heat, radiation, and proteases. The latter characteristic has led to the term protease-resistant isoform of the prion protein. The protease-resistant isoform has been

proposed to slowly catalyze the conversion of the normal prion protein into the abnormal form.

The term "isoform" in the context of prions means two proteins with exactly the same amino acid sequence, that are folded into molecules with dramatically different tertiary structures. The normal cellular isoform of the prion protein (PrP^C) has a high a-helix content, a low b-sheet content, and is sensitive to protease digestion. The abnormal, disease-causing isoform (PrP^{Sc})has a lower a-helix content, a much higher b-sheet content, and is much more resistant to protease digestion.

As used herein the term "prion diseases" refers to transmissible spongiform encephalopathies. Examples for prion diseases comprise Scrapie (sheep, goat), TME (transmissible mink encephalopathy; mink), CWD (chronic wasting disease; muledeer, deer, elk), BSE (bovine spongiform encephalopathy; cows, cattles), CJD (Creutzfeld-Jacob Disease), vCJD, GSS (Gerstmann-Sträussler-Scheinker syndrome), FFI (Fatal familial Insomnia), Kuru, and Alpers Syndrome. Preferred are BSE, vCJD, and CJD.

Immunological diseases

Another aspect of the present invention is directed to the use of at least one compound of the general formula (I) and/or pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of immunological diseases, neuroimmunological diseases, and autoimmune diseases.

Immunological diseases are, for instance, asthma and diabetes, rheumatic and autoimmune diseases, AIDS, rejection of transplanted organs and tissues (cf. below), rhinitis, chronic obstructive pulmonary diseases, osteoporisis, ulcerative colitis, sinusitis, lupus erythematosus, recurrent infections, atopic dermatitis / eczema and occupational allergies, food allergies, drug allergies, severe anaphylactic reactions, anaphylaxis, and other manifestations of allergic disease, as well as uncommon problems such as primary immunodeficiencies, including antibody deficiency states, cell mediated immunodeficiencies (e.g., severe combined immunodeficiency, DiGeorge syndrome, Hyper-IgE syndrome, Wiskott-Aldrich syndrome, ataxia- telangiectasia), immune mediated cancers, and white cell defects.

In autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis (RA), multiple sclerosis (MS), immune-mediated or type 1 diabetes mellitus, immune mediated glomerulonephritis, scleroderma, pernicious anemia, alopecia, pemphigus, pemphigus vulgaris, myasthenia gravis, inflammatory bowel diseases, Crohn's disease, psoriasis, autoimmune thyroid diseases, and Hashimoto's disease, dermatomyositis, goodpastture syndrome, myasthenia gravis pseudoparalytica, ophtalmia sympatica, phakogene uveitis, chronical agressivce hepatitis, primary billiary cirrhosis, autoimunehemolytic anemy, Werlof disease, specific cells uncontrollably attack the body's own tissues and organs (autoimmunity), producing inflammatory reactions and other serious symptoms and diseases.

Hashimoto's thyroiditis is one of the most common autoimmune diseases. "Autoimmune disease" refers to a category of more than 80 chronic illnesses, each very different in nature, that can affect everything from the endocrine glands (like the thyroid) to organs like the kidneys, as well as to the digestive system.

There are many different autoimmune diseases, and they can each affect the body in different ways. For example, the autoimmune reaction is directed against the brain in multiple sclerosis and the gut in Crohn's disease. In other autoimmune diseases such as systemic lupus erythematosus (lupus), affected tissues and organs may vary among individuals with the same disease. One person with lupus may have affected skin and joints whereas another may have affected skin, kidney, and lungs. Ultimately, damage to certain tissues by the immune system may be permanent, as with destruction of insulin-producing cells of the pancreas in Type 1 diabetes mellitus.

Bipolar and clinical disorders

Another aspect of the present invention is directed to the use of at least one compound of the general formula (I) and/or pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of bipolar and clinical disorders.

The term "bipolar and clinical disorders" shall refer to adjustment disorders, anxiety disorders, delirium, dementia, amnestic and other cognitive disorders, disorders usually first diagnosed in infancy, childhood, or adolescence, dissociative disorders, eating disorders, factitious disorders, impulse-control disorders, mental disorders due to a general medical condition, mood disorders, other conditions that may be a focus of clinical attention, personality disorders,

schizophrenia and other psychotic disorders, sexual and gender identity disorders, sleep disorders, somatoform disorders, substance-related disorders, generalized anxiety disorder, panic disorder, phobia, agoraphobia, obsessive-compulsive disorder, stress, acute stress disorder, anxiety neurosis, nervousness, phobia, posttraumatic stress disorder, posttraumatic stress disorder (PTSD), abuse, ADHD, obsessive-compulsive disorder (OCD), manic depressive psychosis, specific phobias, social phobia, adjustment disorder with anxious features.

Examples for anxiety disorders are: acute stress disorder, agoraphobia without history of panic disorder, anxiety disorder due to general medical condition, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, specific phobia, social phobia, substance-induced anxiety disorder.

Examples for delirium, dementia, amnestic and other cognitive disorders are: delirium due to a general medical condition, substance intoxication delirium, substance withdrawal delirium, delirium due to multiple etiologies, Alzheimer's, Creutzfeldt-Jakob disease, head trauma, Huntington's disease, HIV disease, Parkinson's disease, Pick's disease, substance-induced persisting, vascular, dementia due to other general medical conditions, dementia due to multiple etiologies, amnestic disorder due to a general medical condition, substance-induced persisting amnestic disorder.

Examples for disorders usually first diagnosed in infancy, childhood, or adolescence are: mental retardation, learning disorders, mathematics disorder, reading disorder, disorder of written expression, learning disorder, motor skills disorders, developmental coordination disorder, communication disorders, expressive language disorder, phonological disorder, mixed receptive-expressive language disorder, stuttering, pervasive developmental disorders, Asperger's disorder, autistic disorder, childhood disintegrative disorder, Rett's disorder, pervasive developmental disorder, attention-deficit/hyperactivity disorder (ADHD), conduct disorder, oppositional defiant disorder, feeding disorder of infancy or early childhood, pica, rumination disorder, tic disorders, chronic motor or vocal tic disorder, Tourette's disorder, elimination disorders, encopresis, enuresis, selective mutism, separation anxiety disorder, reactive attachment disorder of infancy or early childhood, stereotypic movement disorder.

Examples for dissociative disorders are: dissociative amnesia, depersonalization disorder, dissociative fugue and dissociative identity disorder.

Examples for eating disorders are anorexia nervosa and bulimia nervosa.

Examples for mood disorders are: mood episodes, major depressive episode, hypomanic episode, manic episode, mixed episode, depressive disorders, dysthymic disorder, major depressive disorder, single episode, recurrent, bipolar disorders, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder.

Examples for schizophrenia and other psychotic disorders are: schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, delusions, hallucinations, substance-induced psychotic disorder.

Examples for sexual and gender identity disorders are: female sexual arousal disorder, orgasmic disorders, premature ejaculation, sexual pain disorders, dyspareunia, vaginismus, sexual dysfunction due to a general medical condition, female dyspareunia, female hypoactive sexual desire disorder, male erectile disorder, male hypoactive sexual desire disorder, male dyspareunia, other female sexual dysfunction, other male sexual dysfunction, substance-induced sexual dysfunction, sexual dysfunction, paraphilias, exhibitionism, fetishism, frotteurism, pedophilia, masochism, sadism, transvestic fetishism, voyeurism, paraphilia, gender identity disorder.

Examples for sleep disorders are: dyssomnias, breathing-related sleep disorder, circadian rhythm sleep disorder, hypersomnia, hypersomnia related to another mental disorder, insomnia, insomnia related to another mental disorder, narcolepsy, dyssomnia, parasomnias, nightmare disorder, sleep terror disorder, sleepwalking disorder, parasomnia.

Examples for somatoform disorders are: body dysmorphic disorder, conversion disorder, hypochondriasis, pain disorder, somatization disorder, undifferentiated somatoform disorder.

Examples for substance-related disorders are: alcohol related disorders, amphetamine related disorders, caffeine related disorders, cannabis related disorders, cocaine related disorders, hallucinogen related disorders, inhalant related disorders, nicotine related disorders, opioid related disorders, psychotic

disorder, psychotic disorder, phencyclidine-related disorder, abuse, persisting amnestic disorder, anxiety disorder, persisting dementia, dependence, intoxication, intoxication delirium, mood disorder, psychotic disorder, withdrawal, withdrawal delirium, sexual dysfunction, sleep disorder.

Cardiovascular diseases

The inventive compounds are also useful for prophylaxis and/or treatment of cardiovascular diseases such as adult congenital heart disease, aneurysm, stable angina, unstable angina, angina pectoris, angioneurotic edema, aortic valve stenosis, aortic aneurysm, arrhythmia, arrhythmogenic right ventricular dysplasia, arteriosclerosis, arteriovenous malformations, atrial fibrillation, Behcet syndrome, bradycardia, cardiac tamponade, cardiomegaly, congestive cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, cardiovascular disease prevention, carotid stenosis, cerebral hemorrhage, Churg-Strauss syndrome, diabetes, Ebstein's Anomaly, Eisenmenger complex, cholesterol embolism, bacterial endocarditis, fibromuscular dysplasia, congenital heart defects, heart diseases, congestive heart failure, heart valve diseases, heart attack, epidural hematoma, hematoma, subdural, Hippel-Lindau disease, hyperemia, hypertension, pulmonary hypertension, hypertrophic growth, left ventricular hypertrophy, right ventricular hypertrophy, hypoplastic left heart syndrome, hypotension, intermittent claudication, ischemic heart disease, Klippel-Trenaunay-Weber syndrome, lateral medullary syndrome, long QT syndrome mitral valve prolapse, moyamoya disease, mucocutaneous lymph node syndrome, myocardial infarction, myocardial ischemia, myocarditis, pericarditis, peripheral vascular diseases, phlebitis, polyarteritis nodosa, pulmonary atresia, Raynaud disease, restenosis, Sneddon syndrome, stenosis, superior vena cava syndrome, syndrome X, tachycardia, Takayasu's arteritis, hereditary hemorrhagic telangiectasia, telangiectasis, temporal arteritis, tetralogy of fallot, thromboangiitis obliterans, thrombosis, thromboembolism, tricuspid atresia, varicose veins, vascular diseases, vasculitis, vasospasm, ventricular fibrillation, Williams syndrome, peripheral vascular disease, varicose veins and leg ulcers, deep vein thrombosis, Wolff-Parkinson-White syndrome.

Preferred are adult congenital heart disease, aneurysms, angina, angina pectoris, arrhythmias, cardiovascular disease prevention, cardiomyopathies, congestive heart failure, myocardial infarction, pulmonary hypertension, hypertrophic growth, restenosis, stenosis, thrombosis and arteriosclerosis.

Proliferative disease

In yet another preferred embodiment, the cell proliferative disease is cancer, which is preferably selected from the group comprising:

The proliferation disorders and cancers are preferably selected from the group comprising adenocarcinoma, choroidal melanoma, acute leukemia, acoustic neurinoma, ampullary carcinoma, anal carcinoma, astrocytoma, basal cell carcinoma, pancreatic cancer, desmoid tumor, bladder cancer, bronchial carcinoma, breast cancer, Burkitt's lymphoma, corpus cancer, CUP-syndrome (carcinoma of unknown primary), colorectal cancer, small intestine cancer, small intestinal tumors, ovarian cancer, endometrial carcinoma, ependymoma, epithelial cancer types, Ewing's tumors, gastrointestinal tumors, gastric cancer, gallbladder cancer, gall bladder carcinomas, uterine cancer, cervical cancer, cervix, glioblastomas, gynecologic tumors, ear, nose and throat tumors, hematologic neoplasias, hairy cell leukemia, urethral cancer, skin cancer, skin testis cancer, brain tumors (gliomas), brain metastases, testicle cancer, hypophysis tumor, carcinoids, Kaposi's sarcoma, laryngeal cancer, germ cell tumor, bone cancer, colorectal carcinoma, head and neck tumors (tumors of the ear, nose and throat area), colon carcinoma, craniopharyngiomas, oral cancer (cancer in the mouth area and on lips), cancer of the central nervous system, liver cancer, liver metastases, leukemia, eyelid tumor, lung cancer, lymph node cancer (Hodgkin's/Non-Hodgkin's), lymphomas, stomach cancer, malignant melanoma, malignant neoplasia, malignant tumors gastrointestinal tract, breast carcinoma, rectal cancer, medulloblastomas, melanoma, meningiomas, Hodgkin's disease, mycosis fungoides, nasal cancer, neurinoma, neuroblastoma, kidney cancer, renal cell carcinomas, non-Hodgkin's lymphomas, oligodendroglioma, esophageal carcinoma, osteolytic carcinomas and osteoplastic carcinomas, osteosarcomas, ovarial carcinoma, pancreatic carcinoma, penile cancer, plasmocytoma, prostate cancer, pharyngeal cancer, rectal carcinoma, retinoblastoma, vaginal cancer, thyroid carcinoma, Schneeberger disease, esophageal cancer, spinalioms, T-cell lymphoma (mycosis fungoides), thymoma, tube carcinoma, eye tumors, urethral cancer, urologic tumors, urothelial carcinoma, vulva cancer, wart appearance, soft tissue tumors, soft tissue sarcoma, Wilm's tumor, cervical carcinoma and tongue cancer.

Preferred are the following cancer types: bladder, breast, central nervous system, colon, gastric, lung, kidney, melanoma, head and neck, ovarian, cervix, glioblastoma, pancreas, prostate, stomach, skin testis, leukemia, Hodgkin's lymphoma, liver and renal cancer.

Diabetes

In yet another preferred embodiment, said diabetes is selected from Type I diabetes or Type II diabetes.

Inflammation

In yet another preferred embodiment, said inflammation is mediated preferably by the cytokines TNF-α, IL-1ß, GM-CSF, IL-6 and/or IL-8.

As described above, the compounds according to general formula (I) are pharmaceutically active agents for prophylaxis and/or treatment of inflammatory diseases. Thus, these compounds are used for the manufacture of a pharmaceutical formulation for prophylaxis and/or treatment of inflammations and inflammatory diseases in mammals, including humans.

Inflammatory diseases can emanate from infectious and non-infectious inflammatory conditions which may result from infection by an invading organism or from irritative, traumatic, metabolic, allergic, autoimmune, or idiopathic causes as shown in the following list.

I. Acute infections
   - A. Viral
   - B. Bacterial

II. Noninfectious causes

III. Chronic (granulomatous) diseases
   - A. Bacterial
   - B. Spirochetal
   - C. Mycotic (Fungal)
   - D. Idiopathic

IV. Allergic, immune, and idiopathic disorders
   - A. Hypersensitivity reactions
   - B. Immune and idiopathic disorders

V. Miscellaneous inflammatory conditions
   - A. Parasitic infections
   - B. Inhalation causes:
     - Acute (thermal) injury
     - Pollution and inhalant allergy
     - Carcinogens
   - C. Radiation injury:
     - Radionecrosis

Thus, the compounds disclosed herein can be used for prophylaxis and/or treatment of inflammations caused by invading organisms such as viruses, bacteria, prions, and parasites as well as for prophylaxis and/or treatment of inflammations caused by irritative, traumatic, metabolic, allergic, autoimmune, or idiopathic reasons.

Consequently, the disclosed compounds are useful for prophylaxis and/or treatment of inflammatory diseases which are initiated or caused by viruses, parasites, and bacteria which are connected to or involved in inflammations.

The following bacteria are known to cause inflammatory diseases: mycoplasma pulmonis (causes e.g. chronic lung diseases (CLD), murine chronic respiratory disease), ureaplasma urealyticum (causes pneumonia in newborns), mycoplasma pneumoniae and chlamydia pneumoniae (cause chronic asthma), C. pneumoniae (causes atherosclerosis, pharyngitis to pneumonia with empyema, human coronary heart disease), Helicobacter pylori (human coronary heart disease, stomach ulcers).

The following viruses are known to cause inflammatory diseases: herpesviruses especially cytomegalovirus (causes human coronary heart disease).

The compounds disclosed herein are useful for prophylaxis and/or treatment of inflammatory diseases caused and/or induced and/or initiated and/or enhanced by the afore-mentioned bacteria or viruses.

Furthermore, the compounds of formula (I) are useful for prophylaxis and/or treatment of inflammatory diseases of the central nervous system (CNS), inflammatory rheumatic diseases, inflammatory diseases of blood vessels, inflammatory diseases of the middle ear, inflammatory bowel diseases, inflammatory diseases of the skin, inflammatory disease uveitis, inflammatory diseases of the larynx.

Examples for inflammatory diseases of the central nervous system (CNS) are algal disorders, protothecosis, bacterial disorders, abscessation, bacterial meningitis, idiopathic inflammatory disorders, eosinophilic meningoencephalitis, feline polioencephalomyelitis, granulomatous meningoencephalomyelitis, meningitis, steroid responsive meningitis-arteritis, miscellaneous meningitis / meningoencephalitis, meningoencephalitis in greyhounds, necrotizing

encephalitis, pug dog encephalitis, pyogranulomatous meningoencephalomyelitis, shaker dog disease, mycotic diseases of the CNS, parasitic encephalomyelitis, prion protein induced diseases, feline spongiform encephalopathy, protozoal encephalitis-encephalomyelitis, toxoplasmosis, neosporosis, sarcocystosis, encephalitozoonosis, trypanosomiasis, acanthamebiasis, babesiosis, leishmaniasis, rickettsial disorders, rocky mountain spotted fever, canine ehrlichiosis, salmon poisoning, viral disorders, aujeszky's disease, borna disease, canine herpes virus encephalomyelitis, canine distemper encephalomyelitis, canine distemper encephalomyelitis in immature animals, multifocal distemper encephalomyelitis in mature animals, old dog encephalitis, chronic relapsing encephalomyelitis, post-vaccinal canine distemper encephalitis, feline immunodeficiency virus, feline infectious peritonitis, feline leukemia virus, infectious canine hepatitis, La Crosse virus encephalitis, parvovirus encephalitis, rabies, post-vaccinal rabies, tick-borne encephalitis in dogs.

Examples for inflammatory rheumatic diseases are rheumatoid arthritis, scleroderma, lupus, polymyositis, dermatomyositis, psoriatic arthritis, ankylosing spondylitis, Reiters's syndrome, juvenile rheumatoid arthritis, bursitis, tendinitis (tendonitis), and fibromyositis.

Examples for inflammatory diseases of blood vessels are vasculitis, autoantibodies in vasculitis, microscopic polyangiitis, giant cell arteritis, Takayasu's arteritis, vasculitis of the central nervous system, thromboangiitis obliterans (Buerger's Disease), vasculitis secondary to bacterial, fungal, and parasitic infection, vasculitis and rheumatoid arthritis, vasculitis in systemic lupus erythematosus, vasculitis in the idiopathic inflammatory myopathies, relapsing polychondritis, systemic vasculitis in sarcoidosis, vasculitis and malignancy, and drug-induced vasculitis.

Examples for inflammatory diseases of the middle ear are acute suppurative otitis media, bullous myringitis, granular myringitis, and chronic suppurative otitis media, which can manifest as mucosal disease, cholesteatoma, or both.

Examples for inflammatory bowel diseases are ulcerative colitis, Crohn's disease.

Examples for inflammatory diseases of the skin are acute inflammatory dermatoses, urticaria (hives), spongiotic dermatitis, allergic contact dermatitis,

irritant contact dermatitis, atopic dermatitis, erythemal multiforme (EM minor), Stevens-Johnson syndrome (SJS, EM major), toxic epidermal necrolysis (TEN), chronic inflammatory dermatoses, psoriasis, lichen planus, discoid lupus erythematosus, and acne vulgaris

Uveitis are inflammations located in and/or on the eye and may be associated with inflammation elsewhere in the body. In most circumstances, patients who have uveitis as part of a disease elsewhere in the body are aware of that illness. The majority of patients with uveitis do not have an apparent associated systemic illness. Causes of uveitis can be infectious causes, masquerade syndromes, suspected immune-mediated diseases, and/or syndromes confined primarily to the eye.

The following viruses are associated with inflammations: human immunodeficiency virus-I, herpes simplex virus, herpes zoster virus, and cytomegalovirus.

Bacterial or spirochetal caused, induced, initiated and/or enhanced inflammations are tuberculosis, leprosy, proprionobacterium, syphilis, Whipple's disease, leptospirosis, brucellosis, and lyme disease.

Parasitic (protozoan or helminthic) caused, induced, initiated and/or enhanced inflammations are toxoplasmosis, acanthameba, toxocariasis, cysticercosis, onchocerciasis.

Examples of inflammatory diseases caused, induced, initiated and/or enhanced by fungi are histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, sporotrichosis, blastomycosis, and cryptococcosis.

Masquerade syndromes are, for instance, leukemia, lymphoma, retinitis pigmentosa, and retinoblastoma.

Suspected immune-mediated diseases can be selected from the group comprising ankylosing spondylitis, Behcet's disease, Crohn's disease, drug or hypersensitivity reaction, interstitial nephritis, juvenile rheumatoid arthritis, Kawasaki's disease, multiple sclerosis, psoriatic arthritis, Reiter's syndrome, relapsing polychondritis, sarcoidosis, Sjogren's syndrome, systemic lupus erythematosus, ulcerative colitis, vasculitis, vitiligo, Vogt Koyanagi Harada syndrome.

Syndromes confined primarily to the eye are, for instance, acute multifocal placoid pigmentary epitheliopathy, acute retinal necrosis, birdshot choroidopathy, Fuch's heterochromic cyclitis, glaucomatocyclitic crisis, lens-induced uveitis, multifocal choroiditis, pars planitis, serpiginous choroiditis, sympathetic ophthalmia, and trauma.

Examples for inflammatory diseases of the larynx are gastroesophageal (laryngopharyngeal) reflux disease, pediatric laryngitis, acute laryngeal infections of adults, chronic (granulomatous) diseases, allergic, immune, and idiopathic disorders and miscellaneous inflammatory conditions.

Pediatric laryngitis is known as acute (viral or bacterial) infection such as laryngotracheitis (croup), supraglottitis (epiglottitis), diphtheria, and noninfectious causes are for example spasmodic croup and traumatic laryngitis.

Acute laryngeal infections of adults are, for instance, viral laryngitis, common upper respiratory infection, laryngotracheitis, herpes simplex, bacterial laryngitis, supraglottitis, laryngeal abscess, and gonorrhea.

Chronic (granulomatous) diseases can be selected from the group comprising bacterial diseases, tuberculosis, leprosy, scleroma, actinomycosis, tularemia, glanders, spirochetal (syphilis) diseases, mycotic (fungal) diseases, candidiasis, blastomycosis, histoplasmosis, coccidiomycosis, aspergillosis, idiopathic diseases, sarcoidosis, and Wegener's granulomatosis.

Allergic, immune, and idiopathic disorders are, for example, hypersensitivity reactions, angioedema, Stevens-Johnson syndrome, immune and idiopathic disorders, infections of the immunocompromised host, rheuatoid arthritis, systeic lupus erythematosus, cicatricial pemphigoid, relapsing polychondritis, Sjogren's syndrome, and amyloidosis.

Miscellaneous inflammatory conditions are, for instance, parasitic infections, trichinosis, leishmaniasis, schistosomiasis, syngamus laryngeus, inhalation laryngitis, acute (thermal) injury, pollution and inhalant allergy, carcinogens, radiation injury, radiation laryngitis, radionecrosis, vocal abuse, vocal-cord hemorrhage, muscle tension dysphonias, and contact ulcer and granuloma.

Transplant rejection

Transplant rejection is when a transplant recipient's immune system attacks a transplanted organ or tissue. No two people (except identical twins) have identical tissue antigens. Therefore, in the absence of immunosuppressive drugs, organ and tissue transplantation would almost always cause an immune response against the foreign tissue (rejection), which would result in destruction of the transplant. Though tissue typing ensures that the organ or tissue is as similar as possible to the tissues of the recipient, unless the donor is an identical twin, no match is perfect and the possibility of organ/tissue rejection remains.

The inventive compounds of general formula (I) are used as immunosuppressive drugs and/or anti-rejection drugs in order to prevent transplant rejection.

One example of transplant rejection is the graft-versus-host-disease (GVHD) that can occur following bone marrow transplant. The donor's immune cells in the transplanted marrow make antibodies against the host's (transplant patient's) tissues and attack the patient's vital organs. Transplant rejections (also known as graft rejection or tissue/organ rejection) may commonly occur when tissue or organs, which need blood supply, are transplanted. Said organs comprise especially inner organs such as heart, heart-lungs, lungs, liver, kidney, pancreas, spleen, skin, tissue, bone marrow, spinal marrow, hormone producing glands, gonads and gonadal glands.

Neurodegenerative diseases

Another aspect of the present invention is directed to the use of at least one compound of the general formula (I) and/or pharmaceutically acceptable salts thereof for prophylaxis and/or treatment of neurodegeneration and neurodegenerative disorders.

Among the hundreds of different neurodegenerative disorders, the attention has been given only to a handful, including Alzheimer disease, Parkinson disease, Huntington disease, and amyotrophic lateral sclerosis.

It is worth to mention that the same neurodegenerative process can affect different areas of the brain, making a given disease appear very different from a symptomatic standpoint.

Neurodegenerative disorders of the central nervous system (CNS) can be grouped into diseases of the cerebral cortex (Alzheimer disease), the basal ganglia (Parkinson disease), the brain-stem and cerebellum, or the spinal cord (amyotrophic lateral sclerosis).

Examples for neurodegeneration and neurodegenerative disorders are Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, AIDS-related dementia, retinitis pigmentosa, spinal muscular atrophy and cerebrellar degeneration, fragile X-associated tremor/ataxia syndrome (FXTAS), progressive supranuclear palsy (PSP), and striatonigral degeneration (SND), which is included with olivopontocerebellear degeneration (OPCD), and Shy Drager syndrome (SDS) in a syndrome known as multiple system atrophy (MSA).

In another aspect of the present invention, the compounds according to the general formula (I) as well as pharmaceutically acceptable salts thereof are used as an inhibitor for a protein kinase, preferably as an inhibitor for a cellular protein kinase. Table 1 shows a list with all currently known cellular protein kinases.
In a preferred embodiment of this aspect said cellular protein kinase is selected from the group consisting of:
Cyclin-dependent protein kinase (CDK), protein kinase C, c-Raf, Akt, CKI, IKKβ, MAP kinases/ERKs, MAP kinases/JNKs, EGF receptor, InsR, PDGF receptor, c-Met, p70S6K, ROCK, Rsk1, Src, Abl, p56Lck, c-kit, CaMk2β, CaMk2δ, CaMk2γ, CSK or GSK-3α and ß.The cyclin-dependent protein kinase can be selected from the group comprising:
CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, CDK11, CrkRS (Crk7, CDC2-related protein kinase 7), CDKL1 (cyclin-dependent kinase-like 1); KKIALRE, CDKL2 (cyclin-dependent kinase-like 2), KKIAMRE, CDKL3 (cyclin-dependent kinase-like 3), NKIAMRE, CDKL4, similar to cyclin-dependent kinase-like 1, CDC2L1 (cell division cycle 2-like 1), PITSLRE B, CDC2L1 (cell division cycle 2-like 1), PITSLRE A, CDC2L5 (cell division cycle 2-like 5), PCTK1 (PCTAIRE protein kinase 1), PCTK2 (PCTAIRE protein kinase 2), PCTK3 (PCTAIRE protein kinase 3) or PFTK1 (PFTAIRE protein kinase 1).

As used herein, a kinase "inhibitor" refers to any compound capable of downregulating, decreasing, suppressing or otherwise regulating the amount and/or activity of a kinase. Inhibition of these kinases can be achieved by any of a variety of mechanisms known in the art, including, but not limited to binding

directly to the kinase polypeptide, denaturing or otherwise inactivating the kinase, or inhibiting the expression of the gene (e.g., transcription to mRNA, translation to a nascent polypeptide, and/or final polypeptide modifications to a mature protein), which encodes the kinase. Generally, kinase inhibitors may be proteins, polypeptides, nucleic acids, small molecules, or other chemical moieties.
As used herein the term "inhibiting" or "inhibition" refers to the ability of an compound to downregulate, decrease, reduce, suppress, inactivate, or inhibit at least partially the activity of an enzyme, or the expression of an enzyme or protein and/or the virus replication.

In a further aspect of the present invention, a method for preventing and/or treating infectious diseases, including opportunistic diseases, in a mammal, especially in a human, is provided, which method comprises administering to the mammal an amount of at least one compound according to the general formula (I), effective to prevent and/or treat said infectious diseases, including opportunistic diseases. In a preferred embodiment of this method, the infectious diseases, including opportunistic diseases, are virally induced infectious diseases. The virally induced infectious diseases, including opportunistic diseases, are caused by retroviruses, hepadnaviruses, herpesviruses, flaviviridae, and/or adenoviruses. In a further preferred embodiment of this method, the retroviruses are selected from lentiviruses or oncoretroviruses, wherein the lentivirus is selected from the group comprising: HIV-1, HIV-2, FIV, BIV, SIVs, SHIV, CAEV, VMV or EIAV, preferably HIV-1 or HIV-2 and wherein the oncoretrovirus is selected from the group consisting of: HTLV-I, HTLV-II or BLV. In a further preferred embodiment of this method, the hepadnavirus is selected from HBV, GSHV or WHV, preferably HBV, the herpesivirus is selected from the group comprising: HSV I, HSV II, EBV, VZV, HCMV or HHV 8, preferably HCMV and the flaviviridae is selected from HCV, West nile or Yellow Fever.

In a further aspect of the present invention, methods for preventing and/or treating infectious diseases including opportunistic diseases, prion diseases, immunological diseases, autoimmune diseases, bipolar disorders, cardiovascular diseases, cell proliferative diseases, diabetes, inflammation, transplant rejections, erectile dysfunction, neurodegenerative diseases, and stroke in a mammal, especially in a human, are provided, which methods comprise administering to the mammal an amount of at least one compound according to the general formula (I) and/or pharmaceutically acceptable salts thereof, effective to prevent and/or treat said infectious diseases including opportunistic diseases, prion diseases, immunological diseases, autoimmune diseases, bipolar disorders, cardiovascular

diseases, cell proliferative diseases, diabetes, inflammation, transplant rejections, erectile dysfunction, neurodegenerative diseases, and stroke.

In further preferred embodiments, the specific diseases addressed as infectious diseases including opportunistic diseases, prion diseases, immunological diseases, autoimmune diseases, bipolar disorders, cardiovascular diseases, cell proliferative diseases, diabetes, inflammation, transplant rejections, erectile dysfunction, neurodegenerative diseases, and stroke are selected from the groups disclosed above.

The compounds shown explicitly in Table 2 are preferred to be used within the methods or indications disclosed herein. Another aspect of the present invention is that at least one compound according to the general formula (I) used as a pharmaceutically active agent may be administered in combination with further therapeutic compounds.

For the indication HIV compounds according to the general formula (I), preferably those falling under the activity range "a" for CDK9 as shown in Table 2, may be administered in combination with anti-retroviral drugs, selected from the following five classes:

1) Nucleoside reverse transcriptase inhibitors (NRTIs),
2) Non-nucleoside reverse transcriptase inhibitors (NNRTIs),
3) Protease inhibitors (PIs),
4) Fusion inhibitors or
5) Immune stimuli.

Thus, another aspect of the present invention relates to drug combinations comprising at least one inventive compound according to general formula (I) and/or pharmaceutically acceptable salts thereof together with at least one anti-retroviral drug, especially at least one of the drugs mentioned above.

The pharmaceutical compositions according to the present invention comprise at least one compound according to the present invention as an active ingredient together with at least one pharmaceutically acceptable (i.e. non-toxic) carrier, excipient and/or diluent. The pharmaceutical compositions of the present invention can be prepared in a conventional solid or liquid carrier or diluent and a conventional pharmaceutically-made adjuvant at suitable dosage level in a known way. The preferred preparations are adapted for oral application. These

administration forms include, for example, pills, tablets, film tablets, coated tablets, capsules, powders and deposits.

Furthermore, the present invention also includes pharmaceutical preparations for parenteral application, including dermal, intradermal, intragastral, intracutan, intravasal, intravenous, intramuscular, intraperitoneal, intranasal, intravaginal, intrabuccal, percutan, rectal, subcutaneous, sublingual, topical, or transdermal application, which preparations in addition to typical vehicles and/or diluents contain at least one compound according to the present invention and/or a pharmaceutical acceptable salt thereof as active ingredient.

The pharmaceutical compositions according to the present invention containing at least one compound according to the present invention and/or a pharmaceutical acceptable salt thereof as active ingredient will typically be administered together with suitable carrier materials selected with respect to the intended form of administration, i.e. for oral administration in the form of tablets, capsules (either solid filled, semi-solid filled or liquid filled), powders for constitution, gels, elixirs, dispersable granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable carrier, preferably with an inert carrier like lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid filled capsules) and the like. Moreover, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated into the tablet or capsule. Powders and tablets may contain about 5 to about 95-weight % of the 4,6-disubstituted pyrimdine derivative according to the general formula (I) or analogues compound thereof or the respective pharmaceutically active salt as active ingredient.

Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among suitable lubricants there may be mentioned boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Suitable disintegrants include starch, methylcellulose, guar gum, and the like. Sweetening and flavoring agents as well as preservatives may also be included, where appropriate. The disintegrants, diluents, lubricants, binders etc. are discussed in more detail below.

Moreover, the pharmaceutical compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimise the therapeutic effect(s), e.g. antihistaminic activity and the like. Suitable dosage forms for sustained release include tablets having layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Liquid form preparations include solutions, suspensions, and emulsions. As an example, there may be mentioned water or water/propylene glycol solutions for parenteral injections or addition of sweeteners and opacifiers for oral solutions, suspensions, and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be present in combination with a pharmaceutically acceptable carrier such as an inert, compressed gas, e.g. nitrogen.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides like cocoa butter is melted first, and the active ingredient is then dispersed homogeneously therein e.g. by stirring. The molten, homogeneous mixture is then poured into conveniently sized moulds, allowed to cool, and thereby solidified.

Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions, and emulsions.

The compounds according to the present invention may also be delivered transdermally. The transdermal compositions may have the form of a cream, a lotion, an aerosol and/or an emulsion and may be included in a transdermal patch of the matrix or reservoir type as is known in the art for this purpose.

The term capsule as recited herein refers to a specific container or enclosure made e.g. of methylcellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredient(s). Capsules with hard shells are typically made of blended of relatively high gel strength gelatins from bones or pork skin. The capsule itself may contain small amounts of dyes, opaquing agents, plasticisers and/or preservatives.

Under tablet a compressed or moulded solid dosage form is understood which comprises the active ingredients with suitable diluents. The tablet may be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation, or by compaction well known to a person of ordinary skill in the art.

Oral gels refer to the active ingredients dispersed or solubilised in a hydrophilic semi-solid matrix.

Powders for constitution refers to powder blends containing the active ingredients and suitable diluents which can be suspended e.g. in water or in juice.

Suitable diluents are substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol, and sorbitol, starches derived from wheat, corn rice, and potato, and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 5 to about 95 % by weight of the total composition, preferably from about 25 to about 75 weight %, and more preferably from about 30 to about 60 weight %.

The term disintegrants refers to materials added to the composition to support break apart (disintegrate) and release the pharmaceutically active ingredients of a medicament. Suitable disintegrants include starches, "cold water soluble" modified starches such as sodium carboxymethyl starch, natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar, cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose, microcrystalline celluloses, and cross-linked microcrystalline celluloses such as sodium croscaramellose, alginates such as alginic acid and sodium alginate, clays such as bentonites, and effervescent mixtures. The amount of disintegrant in the composition may range from about 2 to about 20 weight % of the composition, more preferably from about 5 to about 10 weight %.

Binders are substances which bind or "glue" together powder particles and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose, starches derived from wheat corn rice and potato, natural gums such as acacia, gelatin and tragacanth, derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate, cellulose materials such as methylcellulose, sodium carboxymethylcellulose and hydroxypropylmethylcellulose, polyvinylpyrrolidone,

and inorganic compounds such as magnesium aluminum silicate. The amount of binder in the composition may range from about 2 to about 20 weight % of the composition, preferably from about 3 to about 10 weight %, and more preferably from about 3 to about 6 weight %.

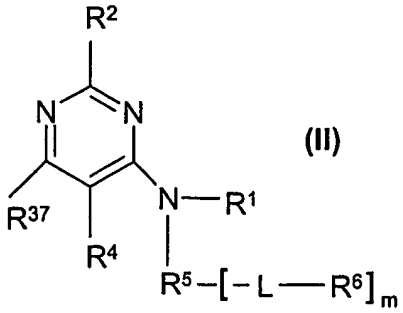
Lubricants refer to a class of substances which are added to the dosage form to enable the tablet granules etc. after being compressed to release from the mould or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate, or potassium stearate, stearic acid, high melting point waxes, and other water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and D,L-leucine. Lubricants are usually added at the very last step before compression, since they must be present at the surface of the granules. The amount of lubricant in the composition may range from about 0.2 to about 5 weight % of the composition, preferably from about 0.5 to about 2 weight %, and more preferably from about 0.3 to about 1.5 weight % of the composition.

Glidents are materials that prevent caking of the components of the pharmaceutical composition and improve the flow characteristics of granulate so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition may range from about 0.1 to about 5 weight % of the final composition, preferably from about 0.5 to about 2 weight %.

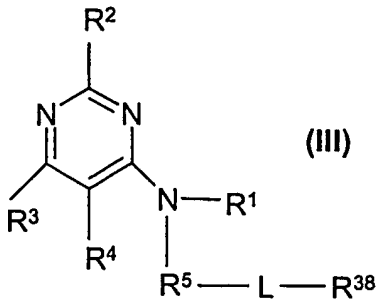
Coloring agents are excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent may vary from about 0.1 to about 5 weight % of the composition, preferably from about 0.1 to about 1 weight %.

Nucleotide-binding proteins play an important role in the metabolism of an organism. E.g., enzymes of the protein kinase family are essential switches of the cellular signal transduction machinery in all eucaryotic cells. They have been implicated with the control of numerous physiological and pathophysiological processes in eucaryotic organisms and therefore represent an important class of drug targets for a variety of indications such as cancer, inflammation and infectious diseases. Efficient and selective enrichment is a prerequisite for subsequent identification of protein kinase targets by a proteomics approach. Efficient pre-fractionation techniques are described in WO 04/013633.

Taking the above-mentioned necessities into account, the present invention provides a **medium** for separating at least one nucleotide binding protein from a pool of proteins, the medium comprises at least one compound of the general formula (II) and/or (III)



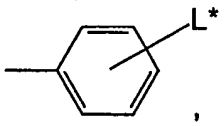
(II)



(III)

wherein

R^1, R^2, R^3, R^4, R^5, R^6, **L** and **m** have the meanings as defined in claim 1,

R^{37} and R^{38} are independently of each other selected from  ,

–L*, substituted or unsubstituted C_1–C_6 alkyl–L*, substituted or unsubstituted C_3–C_8 cycloalkyl–L*, substituted or unsubstituted heterocyclyl–L*, substituted or unsubstituted aryl–L*, or substituted or unsubstituted heteroaryl–L*;

L* is selected from $–X^1–H$, $–X^3$, $–X^1–X^3$;

X^1 and X^2 are independently of each other selected from –NH–, –S–, –O–, –N(C_1–C_6 alkyl)–, –COO–, –O–CO–, –CO–NH–, –NH–CO–, –O–CO–NH–, –NH–CO–O–, –NH–CO–NH–, –O–CO–O–, –NH–C(NH)–NH–, $–NH–SO_2–$, $–SO_2–NH–$;

$X^1–H$ and $Y^1–H$ are independently of each other selected from $–NH_2$, –SH, –OH, –N(C_1–C_6 alkyl)H, –COOH, $–CO–NH_2$, $–O–CO–NH_2$, $–NH–SO_2H$, $–NH–SO_3H$, $–SO_2–NH_2$, $–NH–C(NH)–NH_2$,

X^3 is selected from $–(CH_2)_a–X^4$, $–(CH_2)_a–CO–X^4$, $–(CH_2)_a–NH–SO_2–X^4$, $–(CH_2)_a–Y^1–H$, $–(CH_2)_a–X^2–(CH_2)_b–X^4$, $–(CH_2)_a–X^2–(CH_2)_b–Y^1–H$;

X^4 is selected from –Cl, –Br, –I, $–N_3$, $–OOC–C_1$-C_6 alkyl, $–O–SO_2–CH_3$, $–O–SO_2–p–C_6H_4–CH_3$;

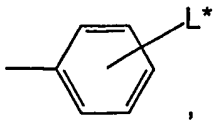
a and **b** are independently of each other interger from 1 – 10;

immobilized on a support material.

It is preferred, that the compounds according to the general formula (II) and/or (III) are covalently bound to the support material. The novel compounds accordint to formula (II) and (III) as well as the the compounds in a form bound to a support material are subject of this invention. Thus, disclosed herewith are also the compounds according to formula (II) or (III) which are not immobilized on a support material. It is clear that to achieve such a covalent bond to the support material one radical, preferably a hydrogen must be replaced in the respective compound to form such a bond with the support material. It is furthermore preferred that these compounds are bonded to the support material via a group Y^1 as defined above. Therefore, all compounds according to the present invention, bearing a $-NH_2$, –SH, –OH, $-N(C_1-C_6$ alkyl)H, –COOH, $-NH-SO_2H$, $-NH-SO_3H$, $-NH-C(NH)-NH_2$ group, can be immobilized on a support material. Especially, all compounds mentioned explicitly in Table 2, bearing a $-NH_2$, –SH, –OH, $-NH(C_1-C_6$ alkyl), –COOH, $-NH-SO_2H$, $-NH-SO_3H$, $-NH-C(NH)-NH_2$ group, can be immobilized on a support material. Said support material comprises preferably sepharose and modified sepharose or can be any other known and common support material, perferably solid support material, which can be used for column chromatography.

In a further preferred embodiment of this medium, R^1, R^2 and R^4 in the compounds according to the general formula (II) and/or (III) are independently of each other selected from –H or linear or branched substituted or unsubstituted C_1-C_4 alkyl;
R^3 represents substituted or unsubstituted phenyl, preferably substituted phenyl, wherein the phenyl is partially or fully substituted with members of the group consisting of: linear or branched C_1-C_4 alkoxy, $-OCH_2-$Phenyl, or $-NH_2$, and wherein phenyl is preferably monosubstituted;
R^5 represents substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, wherein phenyl is preferably substituted with linear or branched substituted or unsubstituted C_1-C_4 alkyl,
L is selected from the group comprising:
$-NH-CO-$, $-NH-SO_2-$, $-SO_2-$, $-SO_2-NH-$ or $-CO-NH-$,
and
m is selected to be 1 and

R^6 is selected from the group comprising: –H, linear or branched substituted or unsubstituted C_1–C_4 alkyl, monosubstituted phenyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroaryl or substituted or unsubstituted C_3–C_8 cycloalkyl, and

R^{37} is selected to be 

,

or wherein

R^{38} is selected from substituted or unsubstituted C_3–C_8 cycloalkyl–L*, preferably unsubstituted C_3–C_8 cycloalkyl–L*, or from substituted or unsubstituted aryl–L*, substituted or unsubstituted C_1–C_6 alkyl–L*, substituted or unsubstituted heterocyclyl–L*, wherein the heterocyclyl is selected from pyrrolidinyl or piperidinyl.

In yet another preferred embodiment of this medium, X^1 in the compounds according to the general formula (II) and/or (III) is selected to be –NH– or –O–, Y^1–H is selected to be $–NH_2$ or –N(C_1–C_6 alkyl)H and preferably $–NH_2$, **a** and **b** are independently of each other selected to be an integer from 1 to 6, preferably from 2 to 4.

In yet another preferred embodiment of this medium, at least one compound according to the general formula (II) and/or (III) immobilized on a support material is selected from the compound list of claim 33 and perferably is 3-Amino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-propionamide (compound 102) and 4-Amino-N-(4-{6-[2-(3-amino-propoxy)-phenyl]-pyrimidin-4-ylamino}-phenyl)-benzamide (compound 103).

In a preferred embodiment of this medium, the support material comprises or consists of sepharose, preferably modified sepharose material like epoxy-activated Sepharose 6B material, obtainable from Amersham Biosciences. Other modified sepharose material which could be used as support material are EAH-sepharose 4B and ECH sepharaose 4C, which can also be obtained by Amersham Biosciences.

According to a still further embodiment of this medium, the support material comprises or consists of ferro- or ferrimagnetic particles as e.g. known from WO 01/71732, incorporated herein by reference as far as properties of ferro- or ferrimagnetic particles are concerned. The ferro- or ferrimagnetic particles may

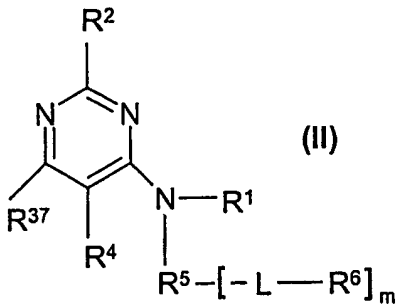
comprise glass or plastic. The ferro- or ferrimagnetic particles that can be used with the present invention may be porous. The ferro- or ferrimagnetic glass particles may comprise about 30 to 50 % by weight of Fe_3O_4 and about 50 to 70 % by weight of SiO_2. The ferro- or ferrimagnetic particles used herein preferably have an average size of about 5 to 25 µm in diameter, more preferably about 6 to 15 µm, and particularly about 7 to 10 µm. The total surface area of the ferro- or ferrimagnetic particles may be 190 m^2/g or greater, e.g. in the range of about 190 to 270 m^2/g (as determined according the Brunaur Emmet Teller (BET) method).

These magnetic particles facilitate purification, separation and/or assay of biomolecules, like protein kinases. Magnetic particles (or beads) that bind a molecule of interest can be collected or retrieved by applying an external magnetic field to a container comprising the particles. Unbound molecules and supernatant liquid can be separated from the particles or discarded, and the molecules bound to the magnetic particles may be eluted in an enriched state.

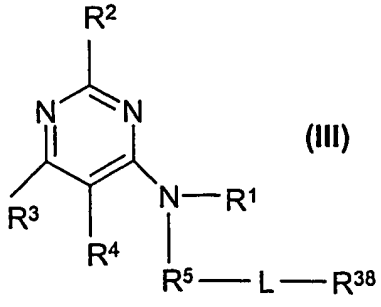
In a still further preferred embodiment of this medium, compounds according to the general formula (II) and/or (III), wherein at least one of those compounds is bound to the support material, can be used to enrich nucleotide binding proteins, preferably an ATP binding protein, more preferably a kinase, and most preferably a protein kinase from a pool of different proteins, like from a proteome, a cell lysate or a tissue lysate.

According to another preferred aspect of the present invention, a method for enriching, purifying or depleting at lest one nucleotide binding protein, preferably an ATP binding protein, more preferably a kinase, and most preferably a protein kinase, from a pool of proteins containing at least one such nucleotide binding protein, wherein the method comprises the following steps:

a) Immobilizing at least one compound of the general formula (II) and/or (III)

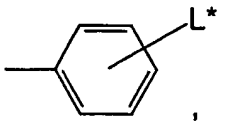


(II)



(III)

wherein
R^1, R^2, R^3, R^4, R^5, R^6, L and m have the meanings as defined in claim 1,

R^{37} and R^{38} are independently of each other selected from 

,

–L*, substituted or unsubstituted C_1–C_6 alkyl–L*, substituted or unsubstituted C_3–C_8 cycloalkyl–L*, substituted or unsubstituted heterocyclyl–L*, substituted or unsubstituted aryl–L*, or substituted or unsubstituted heteroaryl–L*;

L* is selected from $-X^1-H$, $-X^3$, $-X^1-X^3$;

X^1 and X^2 are independently of each other selected from –NH–, –S–, –O–, –N(C_1–C_6 alkyl)–, –COO–, –O–CO–, –CO–NH–, –NH–CO–, –O–CO–NH–, –NH–CO–O–, –NH–CO–NH–, –O–CO–O–, –NH–C(NH)–NH–, $-NH-SO_2-$, $-SO_2-NH-$;

X^1–H and Y^1–H are independently of each other selected from $-NH_2$, –SH, –OH, –N(C_1–C_6 alkyl)H, –COOH, $-CO-NH_2$, $-O-CO-NH_2$, $-NH-SO_2H$, $-NH-SO_3H$, $-SO_2-NH_2$, $-NH-C(NH)-NH_2$,

X^3 is selected from $-(CH_2)_a-X^4$, $-(CH_2)_a-CO-X^4$, $-(CH_2)_a-NH-SO_2-X^4$, $-(CH_2)_a-Y^1-H$, $-(CH_2)_a-X^2-(CH_2)_b-X^4$, $-(CH_2)_a-X^2-(CH_2)_b-Y^1-H$;

X^4 is selected from –Cl, –Br, –I, $-N_3$, –OOC–C_1-C_6 alkyl, $-O-SO_2-CH_3$, $-O-SO_2-p-C_6H_4-CH_3$;

a and b are independently of each other interger from 1 – 10;

on a support material;

b) bringing the pool of proteins containing at least one nucleotide binding protein into contact with at least one compound according to the general formula (II) and/or according to the general formula (III) immobilized on the support material; and

c) separating the proteins not bound to the at least one compound according to the general formula (II) and/or according to the general formula (III) on the

support material from the at least one nucleotide binding protein bound to the at least one said compound immobilized on the support material; and

d) Releasing and collecting the at least one nucleotide binding protein bound to the at least one compound according to the general formula (II) and/or according to the general formula (III) immobilized on the support material from the at least one of said compounds.

According to a preferred embodiment of the method, in the compounds according to the general formula (II) and/or (III), R^1, R^2 and R^4 are independently of each other selected from –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl;

R^3 represents substituted or unsubstituted phenyl, preferably substituted phenyl, wherein the phenyl is partially or fully substituted with members of the group consisting of: linear or branched C_1–C_4 alkoxy, –OCH_2–Phenyl, or –NH_2, and wherein phenyl is preferably monosubstituted;

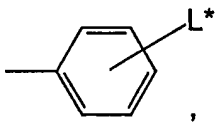
R^5 represents substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, wherein phenyl is preferably substituted with linear or branched substituted or unsubstituted C_1–C_4 alkyl,

L is selected from the group comprising:
–NH–CO–, –NH–SO_2–, –SO_2–NH–, –CO–NH–, –NH–CO–NH–, –NH–CO–O–, –NH–CS–NH–, –NH–C(NH)–NH–, –CO–, –CO–O–, –SO–, –SO_2–, –SO_3– –NR^{14}–SO_2–, –NR^{14}–SO–, –NR^{17}–CO–, –SO_2–NR^{18}–, –CO–NR^{19}–,
wherein R^{14}, R^{17}, R^{18}, and R^{19} have the meanings as defined in claim 1,

and

m is selected to be 1 and

R^6 is selected from the group comprising: –H, linear or branched substituted or unsubstituted C_1–C_4 alkyl, monosubstituted phenyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroaryl or substituted or unsubstituted C_3–C_8 cycloalkyl, and

R^{37} is selected to be 

,

or wherein

R^{38} is selected from substituted or unsubstituted C_3–C_8 cycloalkyl–L*, preferably unsubstituted C_3–C_8 cycloalkyl–L*, or from substituted or unsubstituted aryl–L*, substituted or unsubstituted C_1–C_6 alkyl–L*, substituted or unsubstituted

heterocyclyl–L*, wherein the heterocyclyl is selected from pyrrolidinyl or piperidinyl.

According to a further preferred embodiment of said method, in the compounds according to the general formula (II) and/or (III), $\mathbf{X^1}$ is selected to be –NH– or –O–, $\mathbf{Y^1}$–**H** is selected to be –OH, $-NH_2$ or $-N(C_1-C_6$ alkyl)H, preferably $-NH_2$, and **a** and **b** are independently of each other selected to be an integer from 1 to 6, preferably from 2 to 4.

Preferably, the compounds immobilized on the support material are selected from the compound list of claim 33 and especially preferred are the compopunds 3-Amino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-propion- amide (compound 102) and 4-Amino-N-(4-{6-[2-(3-amino-propoxy)-phenyl]-pyrimidin-4-ylamino}-phenyl)-benz-amide (compound 103).

In yet another preferred embodiment of the present invention, the method further comprises the step of collecting the released at least one nucleotide binding protein, e.g. the ATP binding protein, especially the protein kinase.

The method according to the present invention can be implemented using any of the media and materials described with reference to the first aspect of the present invention.

In a further preferred aspect of the method according to the present invention in step c) the separating of the proteins not bound to the at least one compound immobilized on the support material from the at least one nucleotide binding protein, preferably a ATP binding protein, bound to the at least one compound immobilized on the support material is effected by washing with a buffer containing 5 to 500mM Hepes pH 6.5-8.5 or 5 to 500mM Tris-HCl pH 6.8 to 9.0, 0 to 2500mM NaCl, 0 to 5% Triton X-100, 0 to 500mM EDTA, and 0 to 200mM EGTA. In another preferred embodiment the buffer contains 20mM Hepes/NaOH pH 7.5, 100mM NaCl, 0.15% Triton X-100, 1mM EDTA, and 1mM EGTA.

In yet another preferred embodiment of the method according to the present invention, in step d) the releasing of the at least one nucleotide binding protein, e.g. the protein kinase, bound to the at least one compound immobilized on the support material is effected by washing with a buffer containing 5 to 500mM Hepes pH 6.5-8.5 or 5 to 500mM Tris-HCl pH 6.8 to 9.0, 0 to 1000mM NaCl, 0 to 5.0% Triton X-100, 0-5% SDS, 0 to 500mM EDTA, 0 to 200mM EGTA, 1 to 100mM

ATP, 1 to 200mM $MgCl_2$ and 0.1 to 10mM of at least one of the compounds immobilized on the support material. In another preferred embodiment the buffer contains 50mM Hepes pH 7.5, 150mM NaCl, 0.25% Triton X-100, 1mM EDTA, 1mM EGTA, 10mM ATP, 20mM $MgCl_2$ and 1mM of at least one of the compounds immobilized on the support material.

In yet another preferred embodiment of the method of the present invention, the pool of proteins is a proteome, cell lysate or tissue lysate. In a further embodiment of the method according to the present invention the ATP binding protein is a protein kinase.

In a preferred embodiment of the method according to the present invention, the pool of proteins contains 0.5 to 5M, preferably 0.5 to 3M, and more preferably 0.75 to 2 M of a salt, and preferably is an alkali metal salt, preferably NaCl.

In a preferred embodiment of the present invention, the at least one nucleotide binding protein, preferably a ATP binding protein, is enriched at least 100-fold from the pool of proteins, preferably between 100- and 1000-fold.

In another preferred embodiment the at least one nucleotide binding protein, preferably a ATP binding protein, is enriched at least 10^4-fold and preferably up to 10^6-fold.

In another aspect of the present invention, the invention concerns a kit comprising a medium as outlined above. In a preferred embodiment, the kit further comprises at least one buffer as outlined above.

Description of figures:

Figures 1a-1c show representative compounds of the general formula (I);

Figure 2 shows the kinase activity of different CDK9wt and KRDN (K48R/D167N) amounts;

Figure 3 shows the effect of selected compounds on the dependent Nfκb-transcriptioal activity;

Figure 4 shows the effect of selected compounds on HBV replication;

Figure 5 shows the effect of selected compounds on HCMV replication;

Experimental part:

Analytical methods:

LC/MS data were obtained using a Micromass ZQ instrument with atmospheric pressure chemical ionisation or electrospray ionisation under the conditions described below.

Standard acidic LC-MS conditions (Method A1)

HPLC Setup

Solvents: Acetonitrile (Far UV grade) with 0.1% (V/V) formic acid
Water (High purity via Elga UHQ unit) with 0.1% formic acid

Column: Phenomenex Luna 5μ C18 (2), 30X4.6mm.

Flow Rate: 2ml/min

Gradient: A: Water / formic acid B: MeCN/formic acid

Time	A%	B%
0.00	80	20
2.50	0.00	100
3.50	0.00	100
3.60	80	20
4.50	80	20

Standard acidic LC-MS conditions (Method A2)

HPLC Setup

Solvents: Acetonitrile (Far UV grade) with 0.1% (V/V) formic acid
Water (High purity via Elga UHQ unit) with 0.1% formic acid

Column: Phenomenex Luna 5μ C18 (2), 100 x 4.6mm.

Flow Rate: 2ml/min

Gradient: A: Water / formic acid B: MeCN/formic acid

Time	A%	B%
0.00	95	5
3.50	5	95
5.50	5	95
5.60	95	5
6.50	95	5

UV detection via HP or Waters DAD

Purity is assessed as the integral over the window 210-400 nm.

If necessary, specific wavelength traces are extracted from the DAD data.

Optional ELS detection using Polymer Labs ELS-1000.

MS detection: Either Micromass Platform or ZQ, both single quadrapole LC-MS instruments.

Scan range for MS Data (m/z)

Start (m/z) 100

End (m/z) 650

With +ve / -ve switching

Ionisation is either electrospray or APCI dependent on compound types.

Standard basic LC-MS conditions (Method B1)

HPLC Setup

Solvents: Acetonitrile (Far UV grade)
Water (High purity via Elga UHQ unit) with 10mM ammonium bicarbonate (ammonium hydrogen carbonate)

Column: - Waters Xterra MS 5µ C18, 50 x 4.6mm.

Flow Rate: - 2ml/min

Gradient: - A: Water / NH_4HCO_3 B: MeCN / NH_4HCO_3

Time	A%	B%
0.00	80	20
2.50	0	100
3.50	0	100
3.60	80	20
4.50	80	20

Standard basic LC-MS conditions (Method B2)

HPLC Setup

Solvents: Acetonitrile (Far UV grade)
Water (High purity via Elga UHQ unit) with 10mM ammonium bicarbonate (ammonium hydrogen carbonate)

Column: - Waters Xterra MS 5µ C18, 100 x 4.6mm.

Flow Rate: - 2ml/min

Gradient: - A: Water / NH4HCO3 B: MeCN / NH4HCO3

Time	A%	B%

0.00	95	5
3.50	5	95
5.50	5	95
5.60	95	5
6.50	95	5

UV detection via HP or Waters DAD

Purity is assessed as the integral over the window 210-400 nm.

If necessary, specific wavelength traces are extracted from the DAD data.

Optional ELS detection using Polymer Labs ELS-1000.

MS detection: Either Micromass Platform or ZQ, both single quadrapole LC-MS instruments.

Scan range for MS Data (m/z)

Start (m/z) 100

End (m/z) 650

With +ve / -ve switching

Ionisation is either electrospray or APCI dependent on compound types.

All reagents were obtained commercially and used directly. DMF and THF were dried over 4Å molecular sieves (Fisher Scientific). Column chromatography employed Silica Gel 60 (Fluka). TLC was carried out using pre-coated plastic sheets Polygram SIL G/UV_{254} (Macherey-Nagel).

Standard basic LC-MS conditions (Method C1)

The conditions for the standard basic LC-MS conditions for Method C1 are the same as for Method A1, with the distinction that for method C1 no buffer like ammonium bicarbonate (ammonium hydrogen carbonate) or formic acid was used.

Standard basic LC-MS conditions (Method C2)

The conditions for the standard basic LC-MS conditions for Method C2 are the same as for Method A2, with the distinction that for method C2 no buffer like formic acid was used.

Standard conditions for flash chromatography

Flash chromatography was done using a SiO_2-column and by using the following solvents:

petroleum ether (bp 40 – 60), ethyl acetate, methanol

Standard neutral LC-MS conditions (Method D1)

HPLC Setup

Solvents: Acetonitrile (Lichrosolv Merck)
Water (Lichrosolv Merck) with 1 mM ammonium acetate pH 6.8

Column: - Waters XTerra MS C_{18} 3.5 µm, 3.0 x 50 mm.

Flow Rate: - 0.8 ml/min

Gradient: - A: Water / NH_4OAc B: MeCN

Time	A%	B%
0.00	98	2
5.00	5	95
6.50	5	95
6.60	98	2
8.00	98	2

Standard neutral LC-MS conditions (Method D2)

HPLC Setup

Solvents: Acetonitrile (Lichrosolv Merck)
Water (Lichrosolv Merck) with 1 mM ammonium acetate pH 6.8

Column: - Waters XTerra MS C_{18} 2.5 µm, 3.0 x 30 mm.

Flow Rate: - 0.8 ml/min

Gradient: - A: Water / NH_4OAc B: MeCN

Time	A%	B%
0.00	100	0
1.50	100	0
8.50	30	70
8.60	5	95
10.60	5	95
10.70	100	0
12.00	100	0

Standard neutral LC-MS conditions (Method D3)

HPLC Setup

Solvents: Acetonitrile (Lichrosolv Merck)
Water (Lichrosolv Merck) with 1 mM ammonium acetate pH 6.8

Column: - Bonus RP 3.5 µm, 4.6 x 75 mm.

Flow Rate: - 0.8 ml/min

Gradient: - A: Water / NH_4OAc B: MeCN

Time	A%	B%

0.00	100	0
1.50	100	0
8.50	15	85
8.60	2	98
11.60	2	98
11.70	100	0
13.50	100	0

UV detection via Waters 2996 PDA

For purity assessments the wavelengths at 215, 254 and 310 nm were extracted from the PDA data and an average purity was calculated from the peak areas..

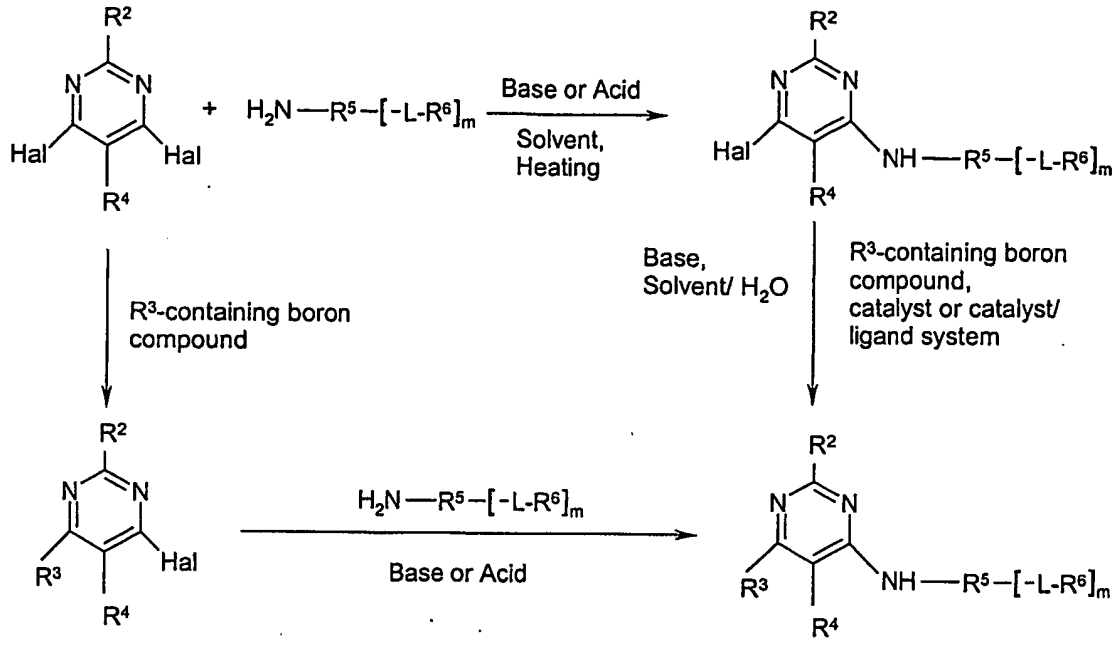
MS detection: Either Micromass Platform or ZQ, both single quadrapole LC-MS instruments.

Scan range for MS Data (m/z)
Start (m/z) 100
End (m/z) 600
With +ve / -ve switching
Ionisation is either electrospray or APCI dependent on compound types.

Syntheses of compounds

The synthesis of the inventive 4,6-disubstituted pyrimidines according to the present invention was preferably carried out according to the general synthetic sequence, shown in **Scheme 1**, involving in a first step amination of the pyrimidine ring followed by Suzuki reaction or an inverse order of the reaction steps:

Scheme 1



Hal represents –Cl, –Br or –I.

R^2 and R^4 have independently of each other the meanings as defined in claim 1, preferably R^2 and R^4 are independently of each other selected from –H, $-NH_2$ or $-CH_3$, R^3, R^5, R^6 and L have the meanings as defined in claim 1, and m is selected to be 0 or 1. In the case protecting groups have been used, a final deprotection step may be follow.

Introduction of the amine moiety can be performed by known methods (J.E. Arrowsmith et al., Journal of Medicinal Chemistry 1989, 32(3), 562-568, J. R. Porter et al, Bioorganic Medicinal Chemistry Letters 2002, 12(12), 1595-1598):

For example, as outlined in Scheme 1, amination is performed by reacting equimolar quantities of 4,6-dihalogenated pyrimidine and an amino compound in a polar solvent, and in the presence of an organic base or an organic or inorganic acid at temperatures in the range of 50 to 120°C. Preferably, the polar solvent is N-methyl-2-pyrrolidinone (NMP) or a lower alcohol, such as iso-propanol or butanol, the organic base is selected for instance from N,N-diisopropylethylamine (DIPEA), N-methyl-piperidine or NEt_3, the acid can be selected for instance from HCl, H_2SO_4, CH_3COOH and the reaction is carried out at a temperature in the range of 60 to 110°C, preferably in the range of 70 to 100°C. It is to be understood, that the reaction temperature depends on the reactivity of the amino compound: For less reactive amino compounds a reaction temperature in the

range of 80 to 110°C is preferred and in these cases a higher boiling solvent such as butanol or NMP affords the desired compounds in good yields.

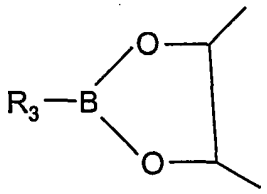
The introduction of R^3 into the pyrimidine scaffold as outlined in Scheme 1, is performed preferably via Suzuki coupling at temperatures in the range of 60 to 110°C, preferably at temperatures in the range of 70 to 100°C, more preferably between 75 to 90°C. (I. Minoru, K. Machiko, T. Masanao, Synthesis 1984, 936-938; J. P. Wolfe, R. A. Singer, B. H. Yang and S. L. Buchwald, Journal of the American Chemical Society 1999, 121, 9550-9561).

The reaction is carried out in organic solvents, such as DME, DMF, THF, Dioxane or methanol or this reaction is carried out in a mixture of an organic solvent and water, such as DMF/water, DME/water or THF/water, in the presence of a base, such as $NaHCO_3$, NaOH, TlOH, NaOMe, K_2CO_3, K_3PO_4, NEt_3, Cs_2CO_3 or Tl_2CO_3 and in the presence of a catalyst, such as $PdCl_2$(dppf) {[1,1'-bis-(diphenylphosphino)ferrocene]dichloropalladium II}, $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ or a catalyst/ligand system, such as $Pd(OAc)_2/PPh_3$, $Pd(OAc)_2$/ 2-(Dicyclohexylphosphino)-biphenyl or $Pd(OAc)_2$/tris(2,4,6-trimethoxyphenyl) phosphine.

The R^3 containing boron compound used for this reaction is selected from the group comprising:

$R_3B(OH)_2$, $R_3B(OPr^i)_2$, R_3-9-BBN

(9-BBN = 9-borabicyclo[3.3.1]nonanyl) or

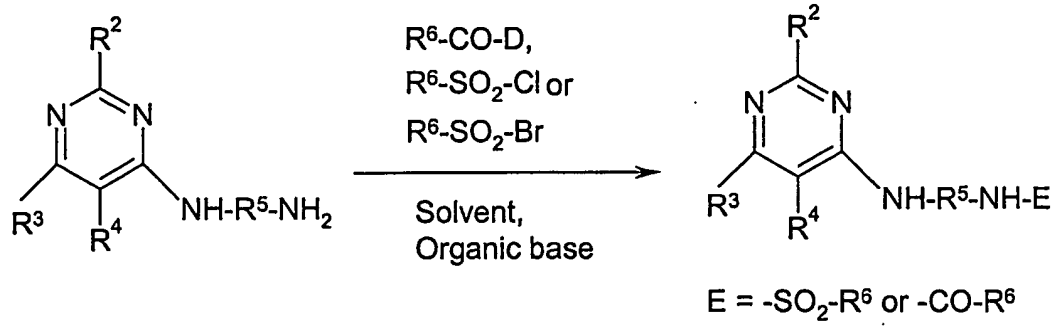


The chemistry described above can be done in either order and further derivatisation can be carried out after amination and before/after subsequent Suzuki cross coupling. Other suitable methods will be apparent to the chemist skilled in the art as will be the methods for preparing the starting materials and intermediates. When protecting groups have been used, optionally a final deprotecting step can be carried out according to general deprotecting reactions known to a person skilled in the art.

For example, inventive compounds according to the present invention, such as amide derivatives, sulfonamide derivatives, urea derivatives or guanidine derivatives can be prepared from suitably functionalised anilines on reaction with

the appropriate reagents. The amide and sulfonamide can be linked as shown in Scheme 2 or the reverse amide can be linked as depicted in Scheme 3. Introduction and removal of protective groups (**PG**) may be necessary for several synthetic steps. This includes for example the use of t-butylcarbamate (BOC) protection for amino acids with standard conditions for introduction and removal.

Scheme 2



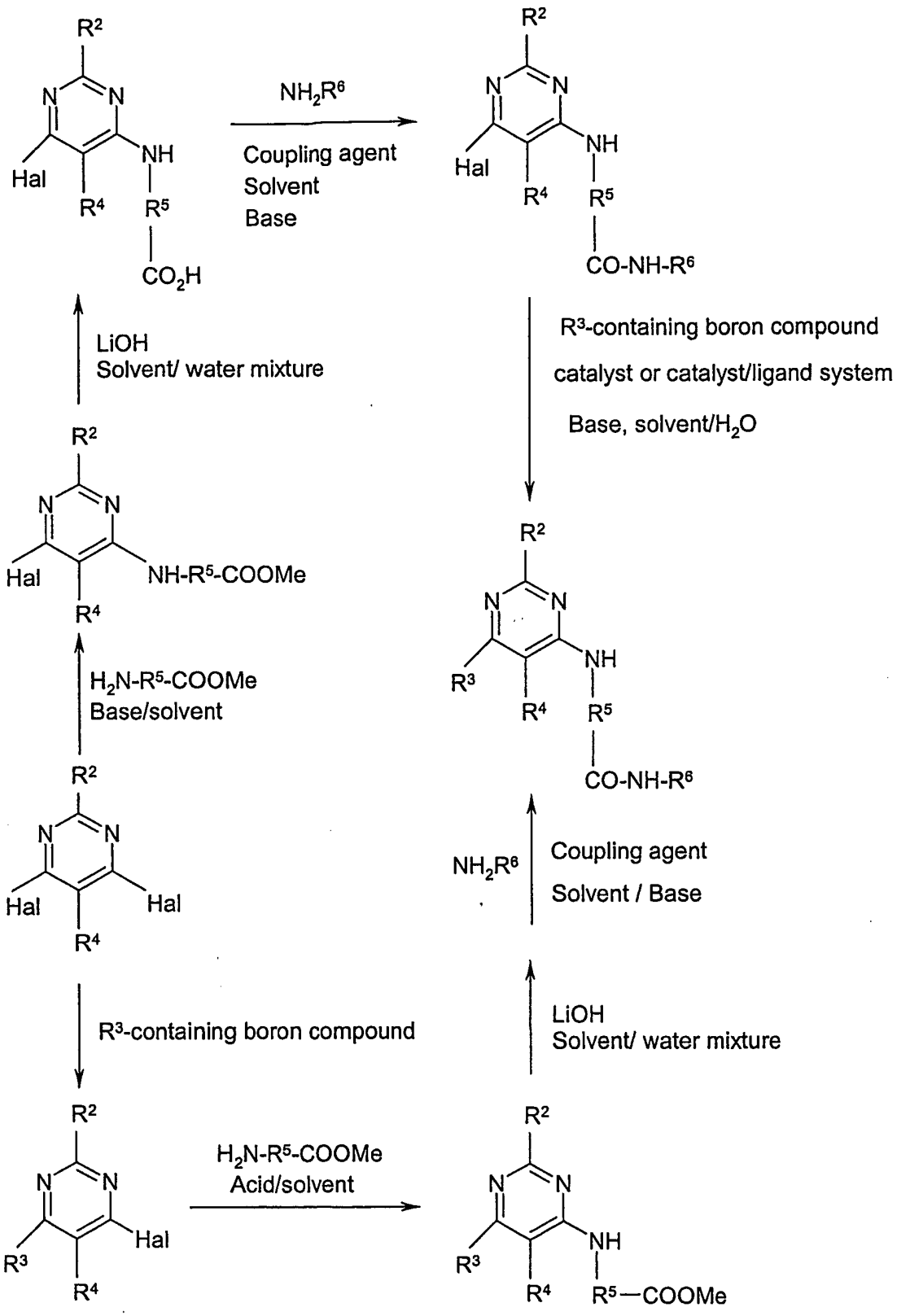
D represents –OH or –Hal.

R^2, R^3, R^4, R^5 and R^6 have the meanings as defined in claim 1, preferably R^2 and R^4 represent –H.

The reaction described in Scheme 2, is carried out in the presence of an inert solvent, such as THF or CH_2Cl_2, in the presence of an organic base, such as NEt_3, DIPEA or 2,4,6-trimethylpyridine (TMP) and at temperatures in the range of –5°C to 60°C, preferably at temperatures in the range of 10 to 50°C, more preferably the reaction is carried out at temperatures between 20 to 45°C. In case D represents –OH, the amine coupling is performed in the presence of a coupling agent, selected from the group comprising: *N*-[(1-H-benzotriazol-1-yl)-dimethylamino)methylene]-*N*-methylmethanaminium hexaflorophopshate *N*-oxide (HBTU), *O*-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)1,1,3,3-tetramethyluronium hexyfluorophosphate (HDTU), *O*-(benzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uranium hexafluorophosphate (HBPipU) or benzotriazol-1-yl-*N*-oxy-tris-(pyrrolidino)phosphonium hexaflurophosphate (PyBOP). Other suitable coupling methods will be apparent to a chemist skilled in the art.

As mentioned above, the reverse amide, can be linked according to the procedure depicted in Scheme 3:

Scheme 3



R^2, R^3, R^4, R^5 and R^6 have the meanings as defined in claim 1, preferably R^2 and R^4 represent –H, and Hal represents –Cl, –Br or –I.

In a first reaction step, a 4,6-dihalogenated pyrimidine is reacted with an amino alkylester compound, wherein the reaction is carried out in the presence of a base, such as DIPEA or acid such as HCl, H_2SO_4, in the presence of a solvent, such as NMP or DMF and at temperatures in the range of 60 to 140°C, preferably at temperatures in the range of 80 to 120°C, more preferably at temperatures in the range of 90 to 110°C.

The second reaction step is carried out in the presence of a base, such as LiOH, and in the presence of solvent/ water mixture selected from the group comprising: THF/water, DME/water or DMF/water. The third reaction step, the amine coupling as shown in Scheme 3, is carried out under the same conditions as described for the correspondent reaction step in Scheme 2.

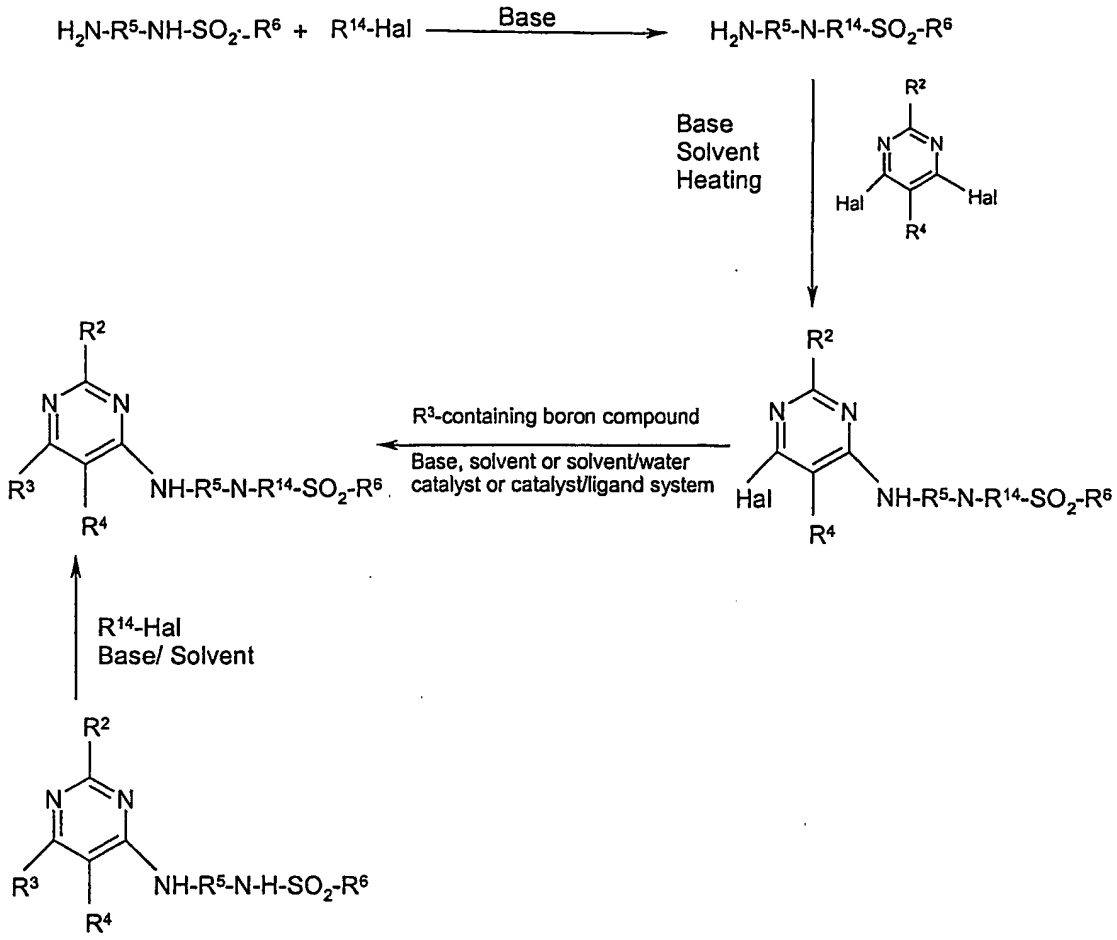
The coupling agent is selected from the group comprising: HBTU, HDTU, HBPipU or PyBOP. Other suitable coupling methods will be apparent to a chemist skilled in the art. The introduction of R^3 into the pyrimidine scaffold is performed as described for the correspondent reaction step in Scheme 1.

According to Scheme 3 the order of reaction steps can also be reversed.

When protecting groups have been used, optionally a final deprotecting step can be carried out according to general deprotecting reactions known to a person skilled in the art.

In Scheme 4, a reaction procedure for the synthesis of alkylated sulfonamide derivatives according to the present invention is shown:

Scheme 4



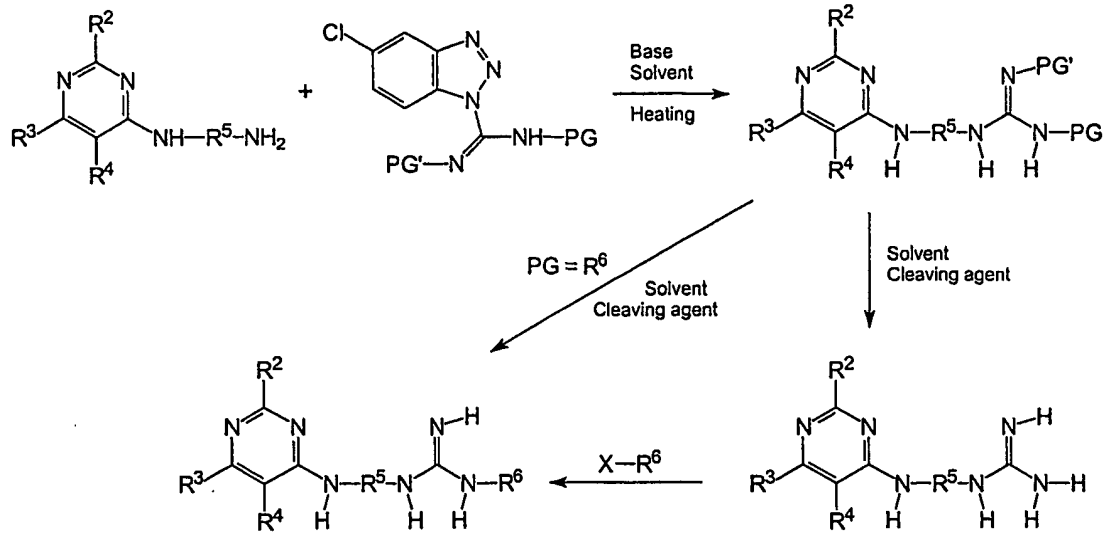
Hal represents –Cl, –Br, or –I.

R^2, R^4, R^5 and R^6 have the meanings as defined in claim 1, preferably R^2 and R^4 represent –H, and R^{14} is selected to be linear or branched substituted or unsubstituted C_1 – C_6 alkyl or $-(CH_2)_r-COOR^{16}$, wherein R^{14}, R^{16} and r have the meanings as defined in claim 1.

Alkylated sulfonamide derivatives according to the present invention can be prepared by reaction of the corresponding sulfonamide with for example an alkyl halide or similar reagent possessing a leaving group in a polar aprotic solvent such as DMF, THF, NMP or Dioxane, in the presence of a strong base such as NaH, $NaNH_2$, $LiNH_2$ or KO^tBu at temperatures in the range of -20 to 80°C, preferably at temperatures in the range of 0 to 60°C, more preferably at temperatures between 20 to 40°C. The obtained intermediates can then be transformed into the desired products as outlined in Scheme 4, whereas the correspondent reaction conditions are described in Scheme 1.

Guanidine derivatives according to the present invention can be prepared by the scheme shown below (H.-J. Musiol and L. Moroder, Organic Letters 2001, 3, 3859-3861):

Scheme 5



R^2, R^3, R^4 and R^5 have the meanings as defined in claim 1, preferably R^2 and R^4 represent –H, and PG represents a protective group, which is defined below. X represents a leaving group such as halogen.

Guanidine derivatives can be prepared by the reaction of an amine compound with a benzotriazole derivative as shown in Scheme 5. This reaction is carried out in the presence of a base, such as NEt_3, DIPEA, N-Methyl-piperidine, or N-Ethyl-Morpholine and an organic solvent, selected from the group comprising: CH_2Cl_2, $CHCl_3$, THF, DMF, dioxane, methyltertbutylether (MTBE) or diisopropylether (DIPE). This reaction is carried out under heating, preferably at a temperature at which the used solvent refluxes.

For the protection of amino acids the protective groups known from peptide chemistry are used. Preferably, carbamate protective groups are used, more preferably a t-butyl carbamate (BOC) group is used.

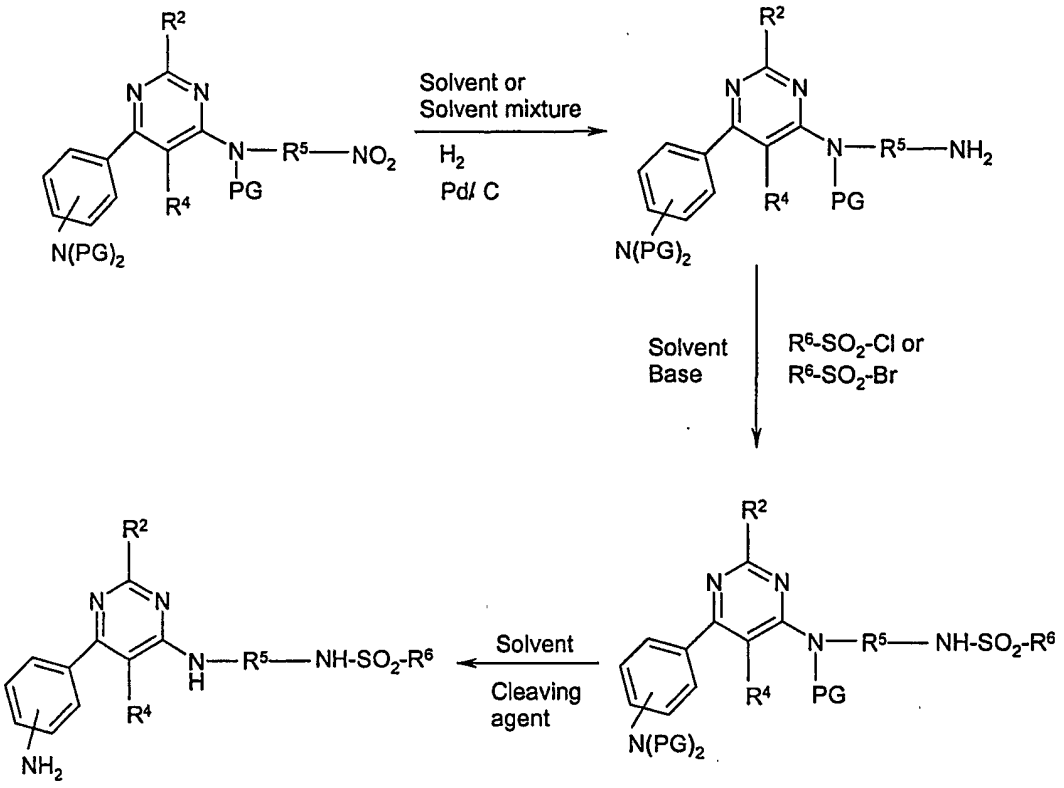
The protective group can be introduced using $(BOC)_2O$, BOC–ONH_2, BOC–N_3 or BOC–O–CHCl–CCl_3, preferably $(BOC)_2O$. The BOC group is introduced under basic conditions in a polar solvent, water or a mixture of water and solvent.

Cleavage of the protective group is performed under acidic conditions, such as HCl in EtOAc, Me_3SiJ in $CHCl_3$, H_2SO_4 in dioxane or trifluroacetic acid in CH_2Cl_2, wherein preferably as cleaving agent/ solvent mixture, trifluroacetic acid in CH_2Cl_2 is used. This reaction is carried out at temperatures in the range of 0 to 60°C,

preferably at temperatures between 10 to 40°C, more preferably at temperatures between 20 to 30°C.

The synthesis of sulfonamide derivatives, wherein R^3 represents aniline, is shown in Scheme 6:

Scheme 6

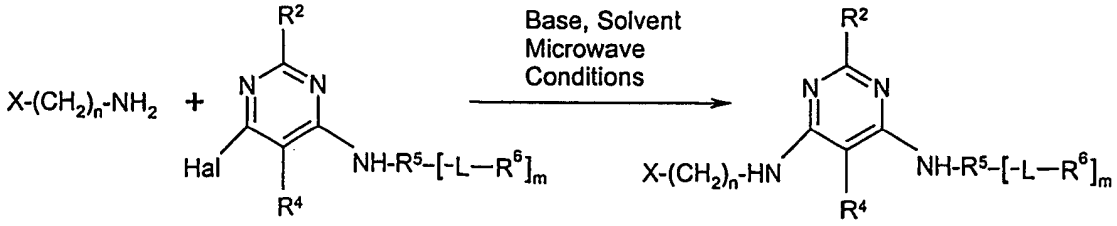


R^2, R^4, R^5 and R^6 are defined as in claim 1, PG as a protective group is defined as above.

The N-protected nitro compound can be synthesized according to the methods described in Scheme 1 and in Scheme 5 (introduction of the protective group). The reduction of the nitro compound is carried out using a standard procedure as described by Ioffe et al, Russian Chemical Review 1966, 35, 19. The solvent can be selected from the group consisting of: MeOH, EtOH, ^{i}PrOH, BuOH or MTBE, and as solvent mixture EtOH/THF can be used. The removal of the protective group is performed as described above (Scheme 5).

For compounds according to the present invention, wherein R^3 represents $-NH-(CH_2)_n-X$, wherein n and X are defined as in claim 1, standard nucleophilic displacement can be carried out as shown in Scheme 1 or with the use of microwave conditions as outlined in Scheme 7 (G. Luo et al., Tetrahedron Letters, 2002, 43, 5739-5743):

Scheme 7



Hal represents –Cl, –Br or –I, R^2, R^4, R^5, R^6, L and m have the meanings as defined in claim 1, preferably R^2 and R^4 are –H.

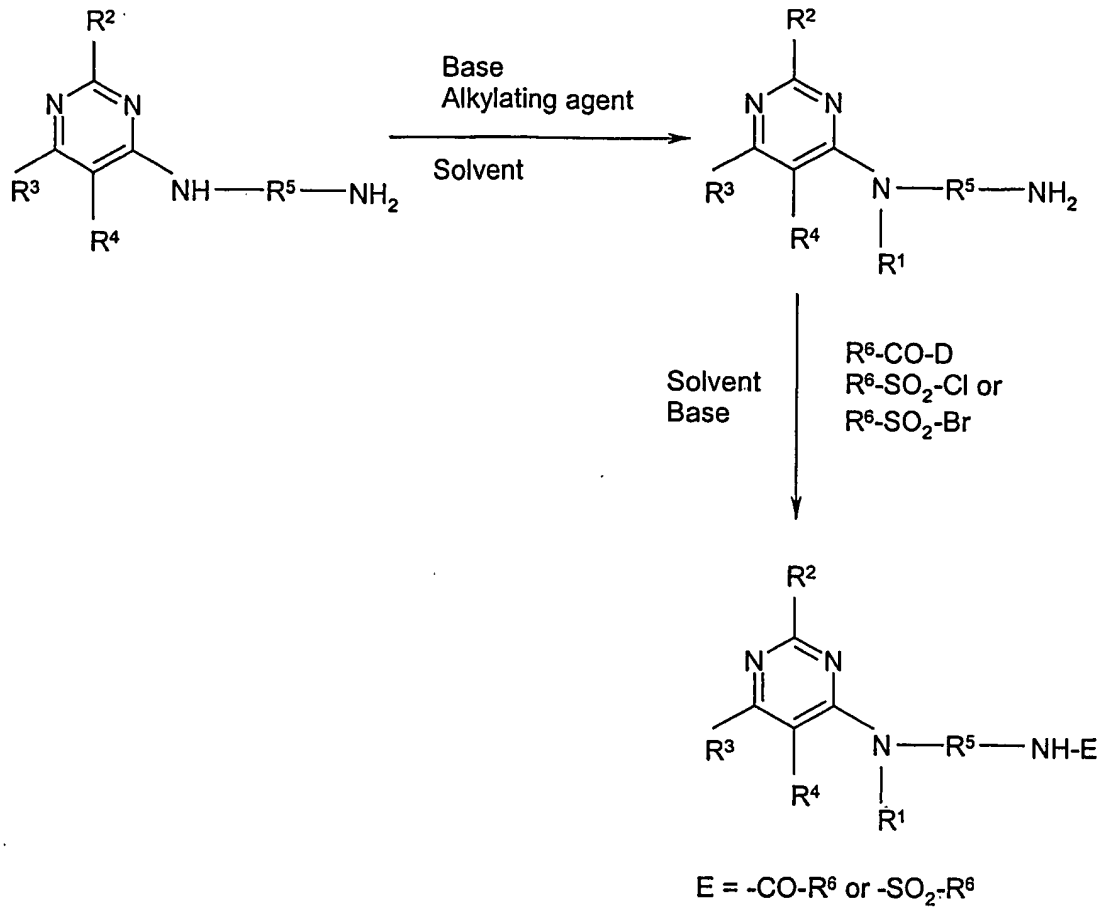
For this reaction an organic base selected from NEt_3, DIPEA or N-methyl-piperidine is used, and the reaction is carried out in a polar solvent such as iso-propanol, butanol or NMP. For the microwave conditions a wattage of 100 to 300, preferably of 150 to 250 watt is used, and the reaction is carried out at temperatures in the range of 140 to 220°C, preferably at temperatures between 150 to 170°C. The preferred reaction time is between 30 min to 140 min.

Compounds according to the present inventions, wherein R^1 represents a linear or branched substituted or unsubstituted C_1 – C_6 alkyl, can be prepared as outlined below:

In a first reaction step, deprotonation of the NH group is achieved, by using a strong inorganic base, such as NaH or an organic base such as Lithiumdiisopropylamid (LDA) or Hexamethyldisilazane (HMDS) and subsequent addition of an alkylating agent, for example an alkyl halide (R^1-halide), alkyl sulfate (R^1-sulfate) or another appropriate leaving group in organic solvents, selected from the group consisting of: DMF, THF, Dioxane, MTBE or DIPE. This reaction is carried out at temperatures in the range of -80 to 60°C, preferably at temperatures in the range of 0 to 40°C, more preferably at temperatures between 20 to 30°C.

The second reaction step is performed under the conditions as described in Scheme 2.

Scheme 8

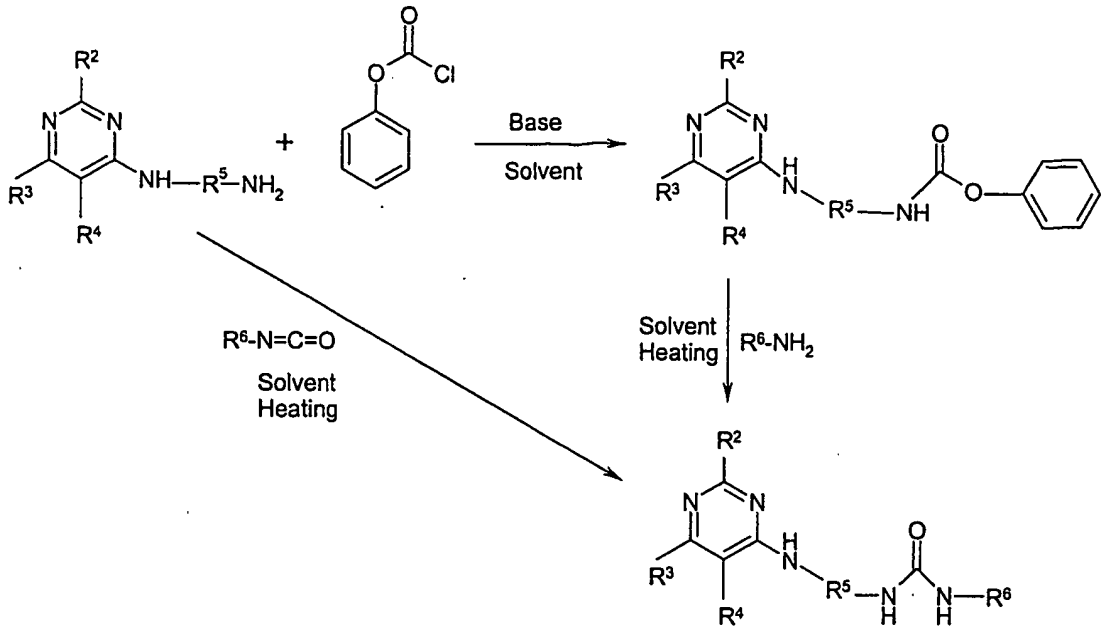


R^2, R^3, R^4, R^5 and R^6 as defined in claim 1, preferably R^2 and R^4 represent –H and D is selected to be –OH or –Hal.

The synthesis of urea derivatives according to the present invention, was carried out according to the two synthetical procedures, depicted in **Scheme 9:**

The urea derivative can be obtained by reacting an amine compound with an isocyanate using a solvent such as dioxane and using temperatures in the range of 60 to 100°C, preferably in the range of 70 to 90°C.

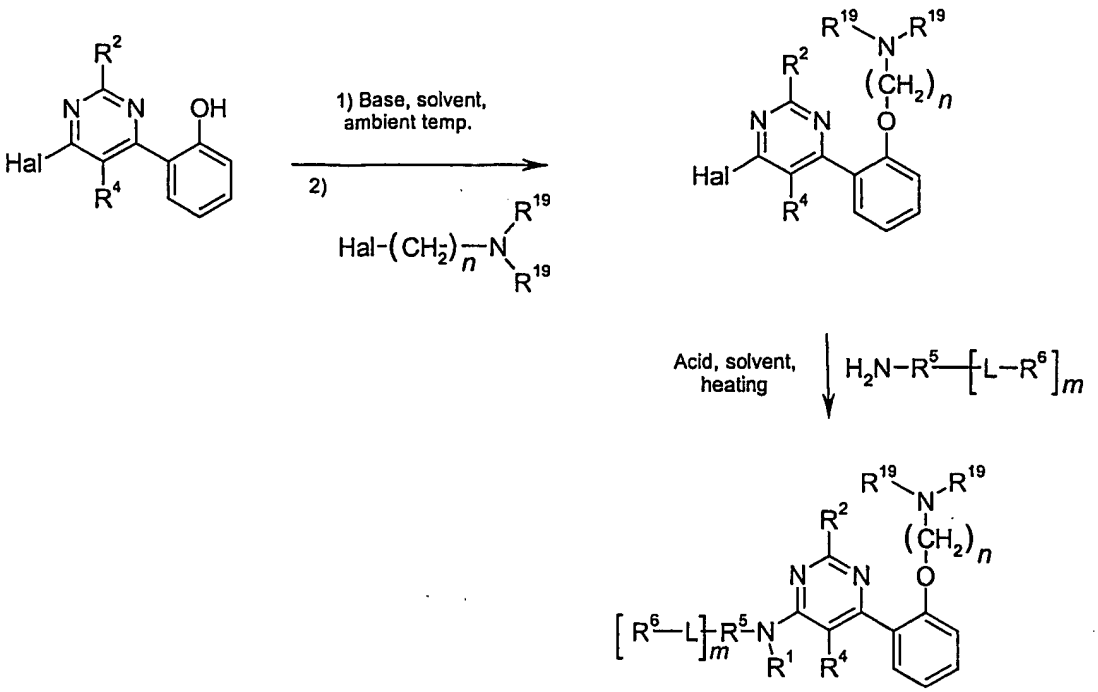
Scheme 9



R^2, R^3, R^4, R^5 and R^6 have the meanings as defined in claim 1.

The second synthetic procedure starts by reacting an amine compound with an equimolar amount of phenyl chloroformate, whereas this reaction is carried out in the presence of a base, such as pyridine, NEt_3 or DIPEA, and a solvent, such as THF, DMF, Dioxane or MTBE. The reaction is performed at a temperature in the range of 0 to 60°C, preferably at a temperature in the range of 10 to 40°C, more preferably between 20 to 30°C. In a second reaction step, a R^6-containing amine compound is reacted with the carbamate derivative to obtain the desired product. This reaction is performed in a solvent such as THF, DMF, Dioxane or MTBE and the reaction is carried out at temperatures in the range of 20 to 100°C, preferably at temperatures in the range of 30 to 80°C, more preferably at temperatures in the range of 40 to 60°C.

Scheme 9A



R^2, R^4, R^5, R^6, R^{19}, L and m have the meanings as defined in claim 1, preferably R^2 and R^4 represent –H. *n* is selected to be 1-8.

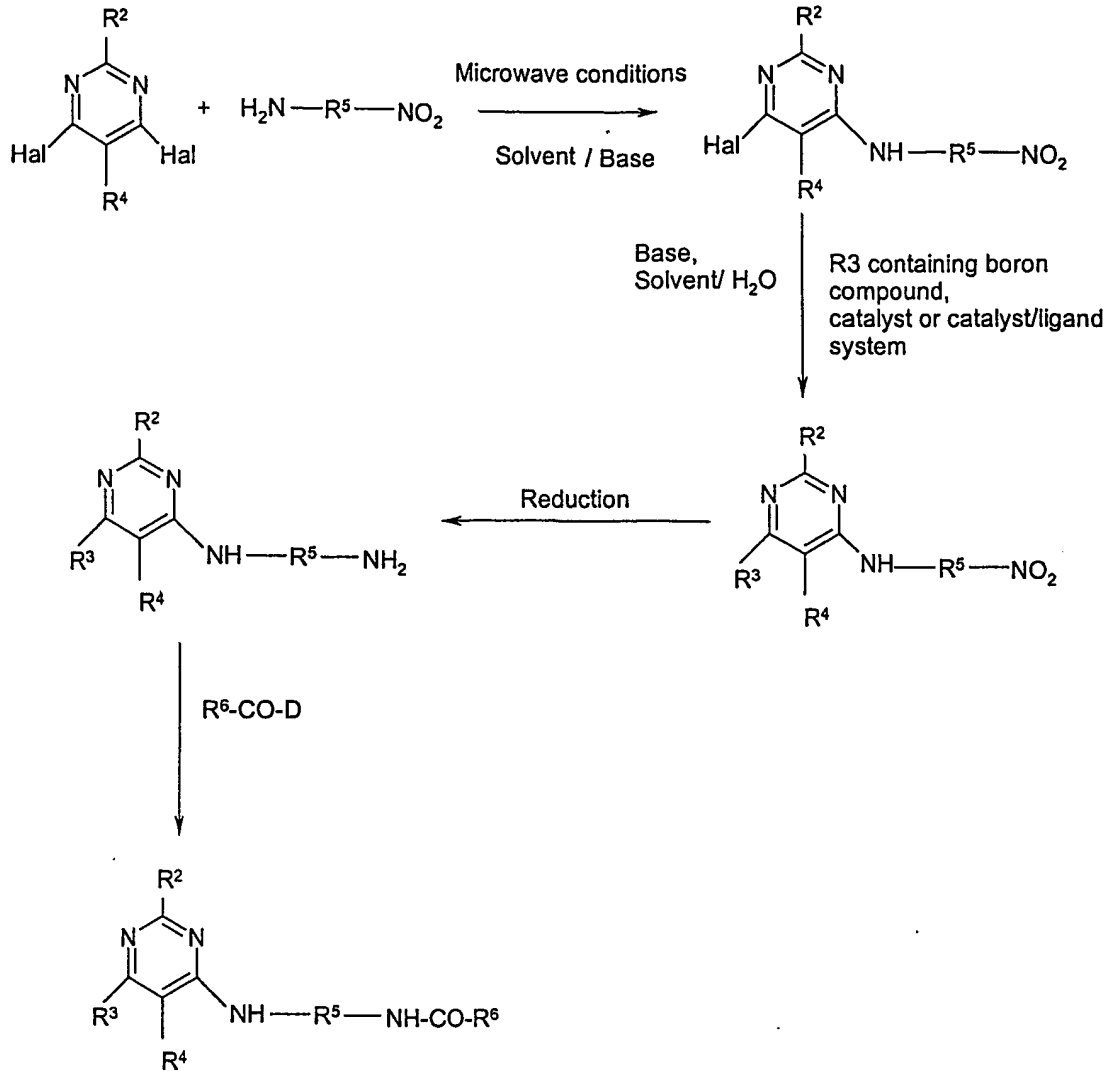
NaH is used as a base in organic solvents, such as THF and DMF. Amination is carried out under acid catalysis according to scheme 1.

The synthesis of amide derivatives according to the present invention, using a different method for the amination step is shown in Scheme 10.

The amination reaction is carried out in a polar solvent, using 1 equivalent of the nitro-aniline derivative and 2 equivalent of the 4,6-dihalogenated pyrimidine derivative in the presence of a base. Preferably, the polar solvent is N-methyl-2-pyrrolidinone (NMP) or a lower alcohol, such as iso-propanol or butanol, the organic base is selected from N,N-diisopropylethylamine (DIPEA), N-methyl-piperidine or NEt_3. This reaction is performed using the following microwave conditions as described by G. Luo et al, Tetrahedron Letters 2002, 43, 5739-5743.

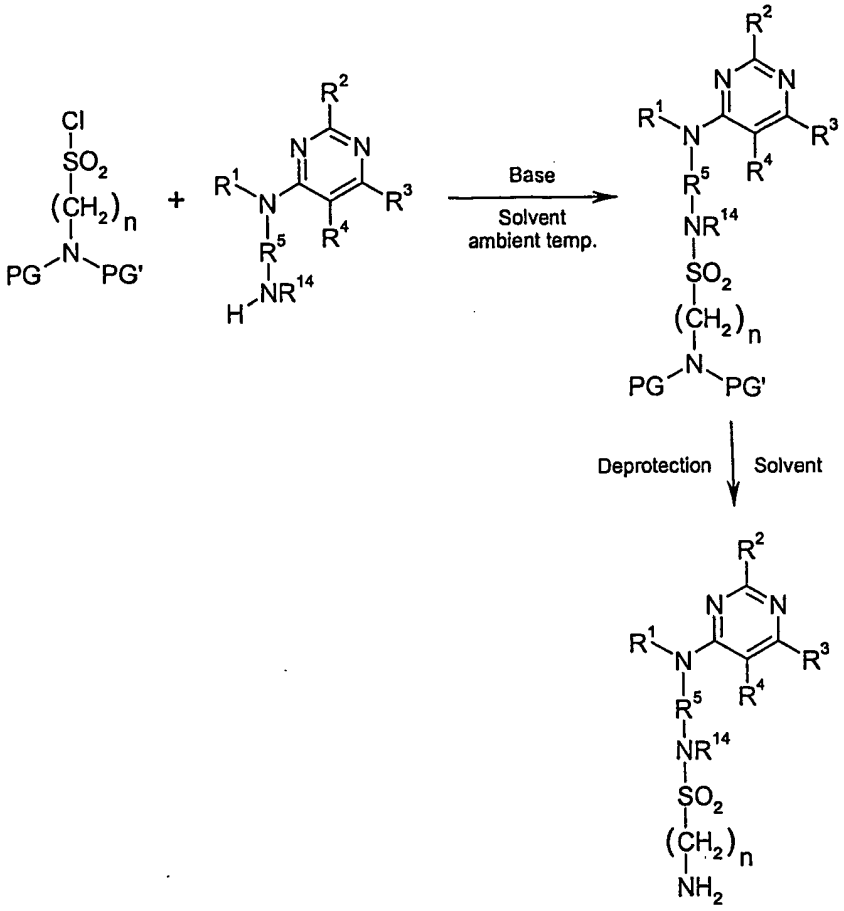
As a next reaction step, a Suzuki coupling is done, under the conditions as described in Scheme 1. The following reduction step can be performed as described by Ioffe et al., Russian Chemical Review 1966, 35, 19. The last reaction step is analogue to the one depicted in Scheme 2.

Scheme 10



R^2, R^3, R^4, R^5 and R^6 have the meanings as defined in claim 1, D is defined as in Scheme 2 and Hal is defined as in Scheme 1.

Scheme 10A



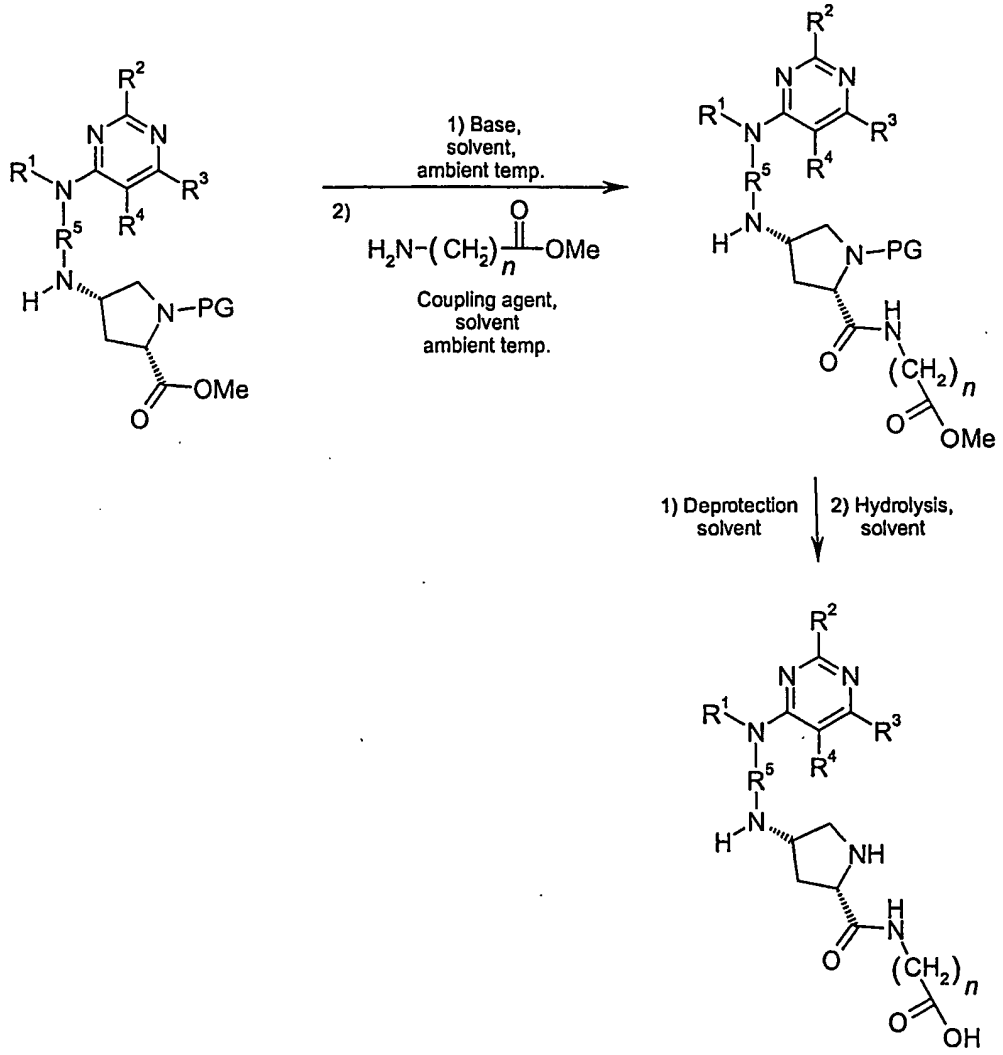
R^1, R^2, R^3, R^4, R^5 and R^{14} have the meanings as defined in claim 1, preferably R^2 and R^4 represent –H, and PG and PG' represents protective groups, where either PG = PG' or PG' = H, which is defined below. *n* is selected to be a number between 1 and 8.

For the protection of the amino function, general protective groups are used. Preferably, the phthaloyl protective group is used, but also carbamates, such as a t-butyl carbamate (BOC) or a 9*H*-fluorenyl-9-ylmethyl carbamate (FMOC) group are used.

The phthaloyl group can be introduced using phthalic anhydride, phthalimide-NCO_2Et, or *o*-$(CH_3OOC)C_6H_4COCl$ in organic solvents and at elevated temperatures, preferably using a base. The BOC group can be introduced using $(BOC)_2O$, BOC–ONH_2, BOC–N_3 or BOC–O–CHCl–CCl_3, preferably $(BOC)_2O$. The BOC group is introduced under basic conditions in a polar solvent, water or a mixture of water and solvent. The FMOC group can be introduced using FMOC-Cl, FMOC-N_3, FMOC-OBt (Bt = benzotriazol-1-yl), FMOC-OSu (Su = succinimidyl)

or FMOC-OC_6F_5. The FMOC group is introduced under basic conditions in a polar solvent or a mixture of water and solvent, using $NaHCO_3$ as a base.

Scheme 10B

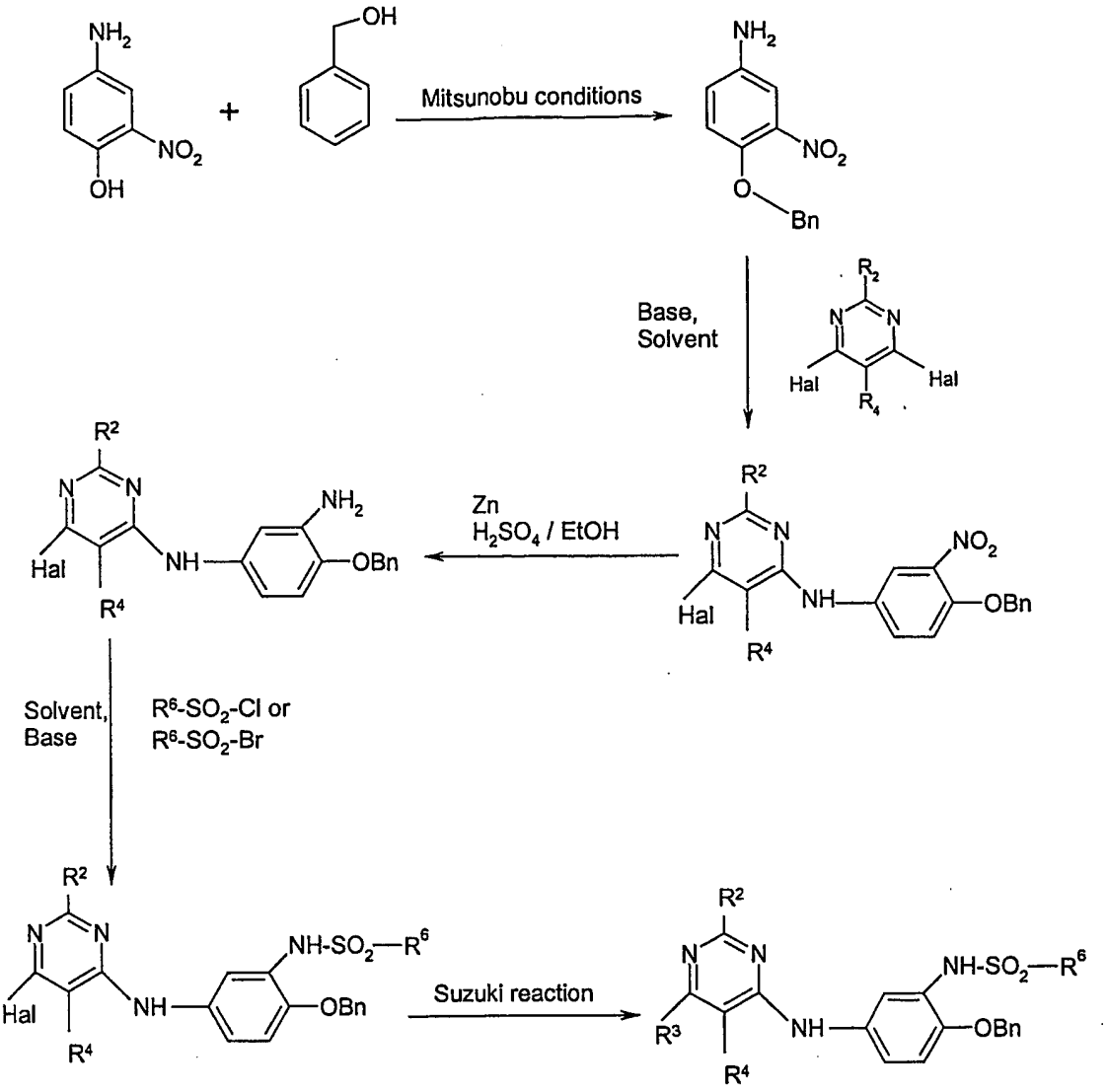


R^1, R^2, R^3, R^4 and R^5 have the meanings as defined in claim 1, preferably R^2 and R^4 represent –H, and PG represents a protective group, preferably a carbamate, such as a *t*-butyl carbamate (BOC) group. *n* is selected to be 1-8.

Hydrolysis of the ester groups is achieved in an organic solvent and water, such as THF/water with a base, such as LiOH. Amide coupling is carried out according to general methods, such as EDC·HCl/HOBt coupling conditions in organic solvents, such as DMF at ambient temperature.

Compounds according to the present invention, wherein L represents –NH–SO_2– can be synthesized as depicted in Scheme 11:

Scheme 11

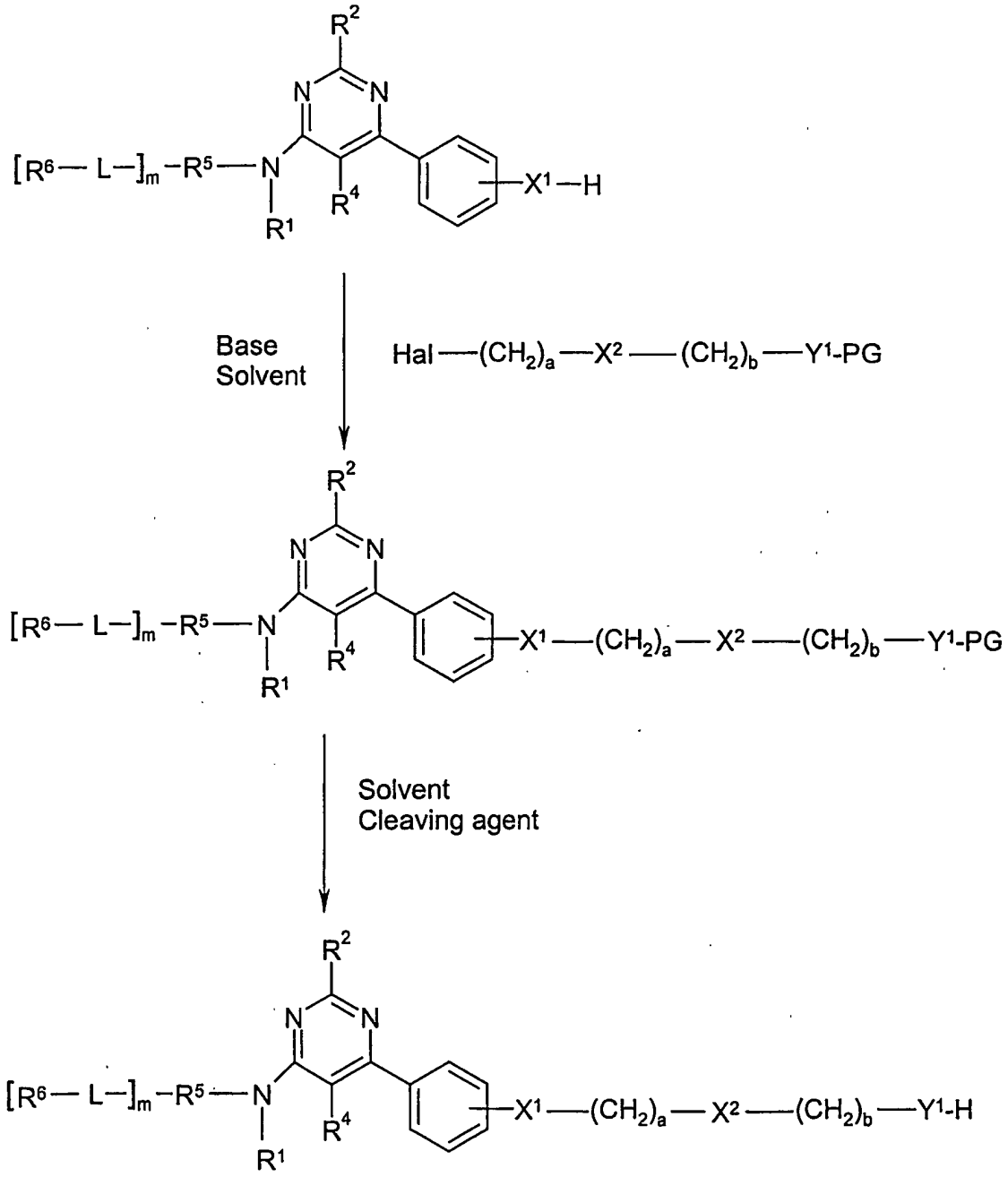


Bn = Benzyl; R^2, R^3, R^4 and R^6 have the meanings as defined in claim 1.

In a first reaction step, a benzylether compound can be synthesized using the conditions as described by O. Mitsunobu et al., Synthesis, 1981, 1-28:
Amino-nitrophenol is reacted with benzylalcohol in the presence of a trialkyl- or triarylphosphine, such as triphenylphsophine and in the presence of a dialkyl azodicarboxylate, such as diethylazo dicarboxylate (DEAD) in a solvent such as Dichloromethane to obtain a benzylether. The amination of this intermediate can be done under the conditions as described in Scheme 1. The following Zn reduction can be performed as described by Ioffe et al., Russian Chemical Review 1966, 35. 19. The last two reaction steps, shown in Scheme 11 can be performed analogously as described in Scheme 2 or in Scheme 1 (Suzuki reaction).

The synthesis of compounds of general formula (II) is depicted in Scheme 12:

Scheme 12



R^1, R^2, R^4, R^5, R^6, L and m have the meanings as defined in claim 1;
X^1 represents –NH–, –S– or –O–, Y^1–H, a and b have the meanings as defined in claim 58, PG represents a protective group as defined in Scheme 6 and Hal represents –Cl, –Br or –I.

In a first reaction step, a pyrimidine derivative is reacted with an alkyl halide derivative according to the scheme below, in a polar aprotic solvent such as DMF, THF, NMP or Dioxane, in the presence of a strong base, such as NaH, $NaNH_2$, , $LiNH_2$ or KO^tBu, at temperatures in the range of 0 to 50°C, preferably at temperatures in the range of 10 to 40°C, more preferably at temperatures between 20 to 30°C.

The obtained intermediates can then be transformed into the desired product by cleaving off the protective group as described for the correspondent reaction step in Scheme 6.

Preparation of compounds:

The LC-MS data for each compound mentioned below are shown explicitly in Table 2.

IA) <u>Preparation of compounds 24, 25 and 72 (according to Scheme 1):</u>

To a solution of 4,6-Dichloropyrimidine (0.67mmol) in ^{i}PrOH (5mL), NEt_3 (1.3mmol) was added at room temperature followed by the amine (0.67mmol) and the mixture was heated at 80°C for 18h. The solvent was then evaporated under reduced pressure and the solid residue suspended in H_2O (~5mL). The solid was separated by filtration washed with water (2x), Et_2O (3x) and then dried to afford the product.

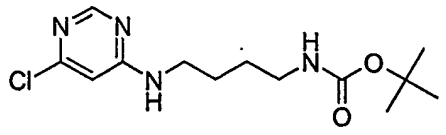
IB) <u>Preparation of compound 309 (according to Scheme 1):</u>

4,6-Dichloropyrimidine (1.5 mmol), methyl 4-aminobenzoate (1.5 mmol), and 3M HCl solution (4 drops) were suspended in ^{i}PrOH (16 ml) and heated in a Personal Chemistry Optimizer microwave system at 100°C for 1200 s. Upon standing at room temperature a precipitate was formed and filtrated off. The solvent of the filtrate was evaporated under reduced pressure and yielded the intermediate in 71% yield as an off-white solid. A suspension of the latter (0.38 mmol), 2-(4,4,5,5,-tetramethyl-1,3,2-dioxyborolan-2-yl)aniline (0.38 mmol), sodium carbonate (1.14 mmol), and $Pd(PPh_3)_2Cl_2$ (2 mol%) in a mixture of DME/EtOH/water (4 ml / 0.5 ml / 0.5 ml) was heated in a Personal Chemistry Optimizer microwave system at 100°C for 1500 s. The reaction mixture was poured into sat. aq. NH_4Cl solution (20 ml) and extracted with EtOAc (3x). The

combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude product was purified by prep.-HPLC (XTerra Prep. MS C_{18} 5 µm, 19 x 150 mm, gradient from water to MeCN over 13 min) and yielded the compound 309 in 37%.

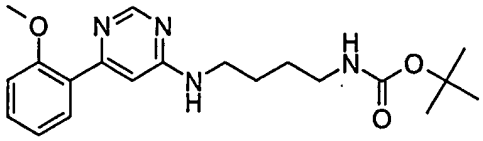
IC) **Preparation of compound 306 (according to Scheme 1):**

a) Preparation of [4-(6-chloro-pyrimidin-4-ylamino)-butyl]-carbamic acid *tert*-butyl ester



4,6-Dichloropyrimidine (4.14 mmol) and *tert*-butyl 4-aminobutylcarbamate (4.14 mmol) were dissolved in 13 ml of 2-propanol, and 3 drops of 3M aq. HCl were added. The mixture was heated in a Personal Chemistry Optimizer microwave system at 100°C for 900 s. The reaction mixture was diluted with sat. aq. NH_4Cl-solution (50 ml) and extracted with EtOAc (2x). Drying of the organic layer (Na_2SO_4) and evaporation of the solvent under reduced pressure yielded the crude product, which was taken up in DMSO (2.5 ml) and purified via prep.-HPLC (XTerra Prep. MS C_{18} 5 µm, 19 x 150 mm, gradient from water to MeCN over 14 min), yielding 41% of a white solid.

b) Preparation of compound 306



The carbamate shown above (0.65 mmol), 2-methoxyphenylboronic acid (0.67 mmol), sodium carbonate (1.95 mmol), and $Pd(PPh_3)_2Cl_2$ (5 mol%) were suspended in a mixture of DMF / EtOH / water (15 ml / 2 ml / 2 ml). The mixture was heated in a Personal Chemistry Optimizer microwave system at 130°C for 720 s. The reaction mixture was diluted with sat. aq. NH_4Cl-solution (50 ml) and extracted with EtOAc (2x). Drying of the organic layer (Na_2SO_4) and evaporation of the solvents under reduced pressure yielded the crude product, which was taken up in DMSO (1.5 ml) and purified via prep.-HPLC (ZORBAX Bonus-RP Prep. C_{18} 5 µm, 21.2 x 150 mm, gradient from water to MeCN over 14 min), yielding 22% of a pale yellow solid.

IIA) **Preparation of compounds 1-17, 18-22, 28, 31, 32, 35, 39, 40, 51, 52, 55-59, 62, 63, 67, 69, 73, 75-77, 85, 92-102, 104-110, 114-119, 121-146, 149-160, 162-193, 197, 200, 202-205, 214, 215, 331-376 (Suzuki coupling according to Scheme 1):**

To a solution of the intermediate obtained according to Preparation method I (0.35mmol) in degassed DMF (5mL), a boron compound (0.38mmol) was added followed by $NaHCO_3$ (0.88mmol) dissolved in degassed H_2O (~1ml), $PdOAc_2$ (0.035mmol) and PPh_3 (0.07mmol). The mixture was then heated at 80-90°C (oil bath temperature) under nitrogen atmosphere for 18h. After being cooled to room temperature, the mixture was diluted with EtOAc (~30mL), washed with H_2O (3x~5mL) and dried ($MgSO_4$). The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography.

The following alternative work up procedure can be used: Upon completion of the reaction, the solvents were evaporated under reduced pressure and the residue was partitioned between EtOAc/H_2O. The H_2O layer was separated and extracted with EtOAc (2x). The combined extracts and the organic layer were dried ($MgSO_4$), the solvent evaporated under reduced pressure and the residue purified by flash chromatography. 2-(Dicyclohexylphosphino)biphenyl was used as a ligand in place of triphenylphosphine in some cases to facilitate the purification procedure.

IIB) **Preparation of compounds 265, 293, 305, 318, 319, 322 (according to Scheme 1):**

4,6-Dichloropyrimidine (0.72mmol), 2-methoxyphenylboronic acid (0.66 mmol), sodium carbonate (1.97 mmol), and $Pd(PPh_3)_2Cl_2$ (3 mol%) were suspended in a mixture of DME / EtOH / water (2.5 ml / 0.38 ml / 0.38 ml). The mixture was heated in a Personal Chemistry Optimizer microwave system at 130°C for 900 s. ^{i}PrOH (5 ml) and the corresponding aniline derivative (0.66 mmol) were added, and the mixture was treated with conc. HCl under stirring to reach a pH value of 1-2. The mixture was then heated in the microwave at 150°C for 900 s. The solvent was evaporated under reduced pressure and the residue suspended in H_2O (10 mL). With sat. $NaHCO_3$ solution the mixture was set to pH = 6-7 and extracted with EtOAc (3x 20 ml). The combined organics were washed with brine and dried over Na_2SO_4. After evaporation of the solvent the residue was taken up in DMSO and purified via prep.-HPLC (XTerra Prep. MS C_{18} 5 µm, 19 x 150 mm, gradient from water to MeCN over 13 min). In the case of products with an acid group in the anilino part, the corresponding methyl esters were prepared via treatment with $TMSCHN_2$ (2-4 eq.) in DCM / MeOH (2 mL / 1 mL) at room temperature.

IIC) Preparation of compounds 268, 307, 313 (according to Scheme 1 & 2):

6-Nitroindoline (1.2 mmol) was dissolved in DCM (8 ml), treated with pyridine (2.4 mmol) and cooled to 0°C. $MeSO_2Cl$ (1.3 mmol) was added dropwise and the mixture allowed to stir at room temperature overnight. 0.5 M HCl solution (10 ml) was added and the mixture extracted twice with DCM (10 ml) and twice with EtOAc (10 ml). The combined organics were washed with brine, dried over Na_2SO_4 and evaporated. The dried residue was dissolved in MeOH (5 ml) and THF (4 ml). Pd/C (100 mg) was added and the mixture stirred under an atmosphere of hydrogen at room temperature for 5 h. The mixture was filtered through a pad of Celite, which was washed with plenty of MeOH and EtOAc. The filtrate was concentrated in vacuum and the residue dried. The crude 6-amino indoline derivative and 4,6-dichloropyrimidine (1.5 mmol) were dissolved in isopropanol (6 ml) and conc. HCl (0.4 ml) and the mixture heated to reflux for 2.5 h. For precipitation of the intermediate product the mixture was stored in the fridge overnight. The precipitate (HCl salt) was filtered, washed with a small quantity of cold isopropanol and dried. The intermediate (0.17 mmol), the corresponding phenylboronic acid (0.2 mmol), Na_2CO_3 (0.58 mmol) and $Pd(PPh_3)_2Cl_2$ (3 mol%) were suspended in a mixture of DME / EtOH / water (1.5 ml / 0.3 ml / 0.2 ml). The mixture was heated in the microwave at 125°C for 1200 s. H_2O (30 ml) was added and the mixture extracted twice with EtOAc (40 ml). Saturated NH_4Cl solution (20 ml) was added to the water phase and extracted again twice with EtOAc (40 ml). The combined organics were washed with brine and dried over Na_2SO_4. After evaporation of the solvent the residue was taken up in DMSO and purified via prep.-HPLC (XTerra Prep. MS C_{18} 5 µm, 19 x 150 mm, gradient from water to MeCN over 13 min).

III) Preparation of compounds 29, 36, 37, 41, 42, 45-50, 52, 61, 64, 65, 70, 71, 84, 87, 89 and 97 (amide bond formation according to Scheme 2):

To a solution of an amine compound (0.24mmol) in THF (4mL) at room temperature under nitrogen atmosphere, an acid compound (0.26mmol) was added followed by NEt_3 (0.36mmol) and HBTU (0.25mmol). The mixture was stirred at room temperature for 1h and then at ~40°C (oil bath temperature) for 18h. After being cooled to room temperature, the mixture was diluted with water (~5mL), extracted with EtOAc (3x) and the combined extract dried ($MgSO_4$). The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography.

IV) **Preparation of compounds 23, 33 and 34 (sulfonamide bond formation according to Scheme 2):**

To a mixture of N-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-benzene-1,4-diamine (0.229mmol) in CH_2Cl_2 (6mL) cooled to ~0°C under nitrogen atmosphere, Et_3N (0.274mmol) was added followed by the sulfonyl chloride (0.252mmol). The mixture was allowed to warm to room temperature and then stirred for 60h. The solvent was evaporated under reduced pressure, the residue suspended in water and extracted with EtOAc (3x). Combined extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography to afford the product.

VA) **Preparation of compounds 44, 54, 72, 88, 147, 148, 161, 194-196, 198, 199, 201, 206-213 (according to Scheme 3):**

The ester compound, 4-(6-Chloro-pyirimidin-4-yl-amino)-benzoic acid methyl ester, has been prepared according to the preparation method I. The reaction was performed in NMP as a solvent using $^iPr_2NEt$ as a base at 100-110°C (oil bath temperature) for 18h. The product precipitated after addition of water to the reaction mixture and was separated by filtration, washed with water (2x), diethyl ether (2x) and dried. The ester compound was isolated as a pale brown solid in 77% yield.

δ_H **(d_6 DMSO):** 3.80 (3H, s, COOMe), 6.85 (1H, s), 7.75 (2H, d), 7.90 (2H, d), 8.55 (1H, s), 10.15 (1H, s, NH).

To a solution of 4-(6-Chloro-pyirimidin-4-yl-amino)-benzoic acid methyl ester, (0.1g, 0.38mmol) in THF (3mL), $LiOH \times H_2O$ (0.017g, 0.42mmol) dissolved in H_2O (1mL) was added and the mixture stirred at room temperature for 18h. The reaction mixture was then diluted with H_2O (5mL) and extracted with EtOAc (2x). The water layer was acidified (2.5M HCl) and extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to afford 4-(6-Chloro-pyirimidin-4-yl-amino)-benzoic acid, as a pale yellow solid.

δ_H **(d_6 DMSO):** 6.95 (1H, s), 7.80 (2H, s), 7.95 (2H, s), 8.65 (1H, s) 10.30 (1H, s) 12.75 (1H, bs, COOH)

a) Starting from the above-mentioned 4-(6-Chloro-pyirimidin-4-yl-amino)-benzoic acid the following compounds were synthesized according to the preparation method III:

b) Starting from the above-mentioned 4-(6-Chloro-pyirimidin-4-yl-amino)-benzoic acid amides (compound 72 and compound 88) the following compounds 44 and 54 were synthesized according to preparation method II:

VB) Preparation of compounds 226, 231, 330 (according to Scheme 3):

4,6-Dichloropyrimidine (1.8 mmol), 2-methoxyphenylboronic acid (1.8 mmol), sodium carbonate (5.4 mmol), and $Pd(PPh_3)_2Cl_2$ (2 mol%) were suspended in a mixture of DME/EtOH/water (12 ml / 1.8 ml / 1.8 ml). The mixture was heated in a Personal Chemistry Optimizer microwave system at 130°C for 600 s. The solution was then poured into sat. aq. NH_4Cl solution (25 ml) and extracted with EtOAc (3x). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford the crude product.
This material (1.8 mmol) was dissolved in ^{i}PrOH (10 ml), methyl 4-aminobenzoate (2.4 mmol) and 3M HCl solution (6 drops) were added. The resulting mixture was heated in the microwave at 120°C for 900 s, then cooled to room temperature. The precipitate was filtrated off, washed with ^{i}PrOH and dried. This provided the intermediate in 49% yield (over 2 steps).
Latter compound (1.2 mmol) was subsequently dissolved in THF/water (3 ml/6 ml) and lithium hydroxide (3.58 mmol) was added. Stirring of the reaction mixture at room temperature for 16 h led to total conversion and the solution was set to pH = 1 by addition of 3 M HCl solution. A precipitate was formed and filtration yielded 4-[6-(2-methoxy-phenyl)-pyrimidin-4-yl-amine]-benzoic acid in quantitative yield. This pyrimidine derivative (0.22 mmol) was subsequently reacted with different amines (0.22 mmol) in DMF (1.5 ml) with EDC·HCl (0.28 mmol) and HOBt (0.07 mmol). After stirring for 4-20 h, the reaction was poured into water (15 ml) and extracted with EtOAc (3x). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Purification by prep.-HPLC (XTerra Prep. MS C_{18} 5 µm, 19 x 150 mm, gradient from water to MeCN over 13 min) or flash chromatography (SiO_2) yielded the compounds 231, 226, and 330 with up to 81% yield.

VIA) Preparation of the compounds 26 and 27 (according to Scheme 4 & 8)

To a mixture of N-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-benzene-1,4-diamine (0.68mmol) in DMF (4.6ml) under nitrogen atmosphere at room temperature, NaH (0.75mmol) was added and the mixture stirred for 30min. MeI (0.68mmol) was added dropwise and the reaction mixture stirred for 42h. The mixture was then diluted with H_2O (~7mL) and extracted with EtOAc (3x). The combined extracts

were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was triturated with Et_2O to afford the product as a brown solid.

This compound is prepared according to the procedure described for compound 26, but instead of the diamine compound N-{4-[6-(4-Hydroxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-4-methyl-benzenesulfonamide is used. THF was used as solvent, and 1 eq of Bromoacetic acid methyl ester as alkylating agent. The reaction was performed at 50-60°C (oil bath temperature) for 18h. The crude reaction mixture was purified by flash chromatography to afford the product as a pale yellow solid.

VIB) Preparation of the compounds 234, 327, 328, 329 (according to Scheme 8A)

To a solution of the proline derivative (0.22 mmol) (prepared in analogy to compounds described in M. Tamaki, G. Han, V. J. Hruby, *J. Org. Chem.* **2001**, *66*, 3593-3596; J. A. Gómez-Vidal, R. B. Silverman, *Org. Lett.* **2001**, *3*, 2481-2484; D. J. Abraham, M. Mokotoff, L. Sheh, J. E. Simmons, *J. Med. Chem.* **1983**, *26*, 549-554) and 4-[6-(2-methoxy-phenyl)-pyrimidin-4-yl-amine]-benzoic acid (0.22 mmol) in DMF (1.5 ml) were added EDC·HCl (0.28 mmol) and HOBt (0.07 mmol) and the reaction stirred at room temperature for 4-18 h. The solution was then poured into water (15 ml) and extracted with EtOAc (3x). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude products were purified by flash chromatography (SiO_2, c-hexane/EtOAc, 1:2) and gave compound **234** in 40% yield.

Compound 234 (0.16 mmol) was dissolved in DCM (4 ml) and treated with TFA (4 ml). After stirring at room temperature for 1 h, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (SiO_2, DCM/MeOH 95:5 + 0.5 vol% NEt_3) yielding compound **327** in 76%. Subsequent reaction of compound 327 (0.11 mmol) in THF/water 1:2 with LiOH (0.44 mmol) at room temperature for 48 h gave after purification by prep.-HPLC (ZORBAX Bonus-RP Prep. C_{18} 5 µm, 21.2 x 150 mm, gradient from water to MeCN over 15 min) compound **328**.

To a solution of compound 234 (0.89 mmol) in THF (3 ml) were added water (6 ml) and lithium hydroxide (3.55 mmol) and the reaction was stirred at room temperature for 40 h. The reaction mixture was cooled to 0°C and 3 M HCl solution was added until a precipitate was formed. Filtration and drying of the solid gave the desired intermediate in 88%. The latter (0.19 mmol) was dissolved in DMF (7 ml), methyl 6-aminobenzoate (0.24 mmol), EDC·HCl (0.24 mmol) and HOBt (0.06 mmol) were added and the reaction stirred for 4 h. Another portion of

methyl 6-aminobenzoate (0.12 mmol), EDC·HCl (0.12 mmol) and HOBt (0.03 mmol) was added and the reaction stirred for another 15 h. Water (25 ml) was added and the solution extracted with EtOAc (3x). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Purification by flash chromatography (SiO_2, DCM/MeOH 95:5) yielded the product in 89%. To a solution of this compound (0.024 mmoles) in DCM (1 ml) was added TFA (1 ml) and the reaction stirred at room temperature for 30 min. After evaporation of the solvent under reduced pressure and drying of the resulting oil, the crude product was dissolved in THF (1 ml). Water (2 ml) and lithium hydroxide (1.00 mmol) were added and the reaction was stirred at room temperature for 64 h. The solvent was then evaporated under reduced pressure and the resulting mixture purified by prep.-HPLC (XTerra Prep. MS C_{18} 5 µm, 19 x 150 mm, gradient from water to MeCN over 13 min). Compound **329** was obtained in 73%.

VII) **Preparation of compounds 30, 66, 68, 81-83, 86, 90-91 (according to Scheme 6 by deprotection of protected substituents):**

The BOC-protected compounds can be synthesized according to the reaction protocol as outlined in Scheme 6.

To a solution of N-Boc compound (0.07mmol) in TFA/CH_2Cl_2 (1mL, 1:1) a few drops of water were added and the mixture stirred at room temperature for 2-18h. The reaction mixture was diluted with toluene (5mL) and the solvents were evaporated under reduced pressure. The residue was partitioned between EtOAc/$NaHCO_3$ (saturated aqueous solution), (~15mL, 1:1). The organic layer was separated, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to afford the product.

VIII) **Preparation of compounds 43, 60, 74, 78-80 (according to Scheme 7):**

To a mixture of the 6-Chloro-pyrimidin-4-yl-aryl-amine (0.3mmol) in i-PrOH (1mL) in the microwave tube, amine (0.685g, 0.6mmol) was added followed by $^{i}Pr_2NEt$ (0.6mmol). The reaction mixture was heated under microwave conditions (200W, t = 160°C) for 2h and 15min and then, after being cooled to room temperature, was diluted with EtOAc/H_2O (~12mL, 2:1). The organic layer was separated and the H_2O layer extracted with EtOAc (2x). Combined organic layers were dried ($MgSO_4$), the solvent evaporated under reduced pressure and the residue purified by flash chromatography to afford the product.

IXA) **Preparation of compounds 38 and 111-113 (according to Scheme 9)**

To a suspension of an amine (0.17mmol) in dioxane (2ml), isocyanate (0.19mmol) was added and the mixture was heated at 80-90°C (oil bath temperature) for 24h. The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography to afford product.

An alternative route for synthesizing urea derivatives according to the present invention is described below:

Pyridine (0.7mMol) was added to a suspension of an amine (0.3mMol) as outlined in Scheme 9 in dry THF (3 mL), followed by phenyl chloroformate (0.3mMol). The mixture was stirred at room temperature for 1 hour. The solvent was evaporated and the residue partitioned in EtOAc:H_2O. The organic layer was dried ($MgSO_4$), solvent removed and the obtained carbamate was used in the next step without further purification. An amine compound (0.10mMol) was added to a solution of the carbamate (0.07mMol) in dry THF (2.5 mL) and the mixture was heated at 50°C for 72 hours. After cooling to room temperature, a precipitate appeared which was collected by filtration and washed with Et_2O to afford the desired product in 59% yield and 100% purity by LC/MS

IXB) **Preparation of compounds 292, 323 – 326 (according to Scheme 9A)**

4,6-Dichloropyrimidine (3.7 mmol), 2-hydroxyphenylboronic acid (1.2 mmol), sodium carbonate (3.7 mmol), and $Pd(PPh_3)_2Cl_2$ (2 mol%) were suspended in a mixture of DME/EtOH/water (12 ml / 1.8 ml / 1.8 ml), then heated in a Personal Chemistry Optimizer microwave system at 100°C for 1500 s. The reaction mixture was poured into sat. aq. NH_4Cl solution (40 ml) and extracted with EtOAc (3x). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford the crude product. Flash chromatography yielded the intermediate as light-yellow powder in 68% yield.

To as suspension of NaH (3.10 mmol) in dry DMF (1.0 ml) under nitrogen at 0°C was added a solution of the above described intermediate (0.97 mmol) in dry DMF (1.5 ml). The resulting mixture was stirred at 0°C for 15 min. The corresponding 2-chloro- or 2-bromoethylamines (as hydrochloride or hydrobromide salts) were then added (1.26 mmol) and the reaction stirred at 0°C for 3 h, then the cooling bath removed and the reaction allowed to warm to room temperature. After 4 h, the reaction was diluted with EtOAc (20 ml) and water (10 ml) was carefully added. Extraction with EtOAc (3x) and drying of the combined organic layers (Na_2SO_4) gave after evaporation of the solvent under reduced pressure the crude product.

This intermediate (0.18 mmol) was dissolved without further purification in ^{i}PrOH (2.4 ml), methyl 4-aminobenzoate (0.23 mmol) and 3 M HCl solution (2 drops)

were added and the reaction was heated in a Personal Chemistry Optimizer microwave system at 100°C for 1200 s. The precipitate (if formed upon standing at 4°C for 18 h, otherwise the solvent was evaporated under reduced pressure) was filtrated off and the solid was dissolved in EtOAc (20 ml) and sat. aq. $NaHCO_3$ solution (10 ml). Separation of the organic layer gave after drying (Na_2SO_4) and evaporation of the solvent the crude product. Latter was purified by flash chromatography (SiO_2, DCM/MeOH 14:1 with 0.5 vol% NEt_3) and yielded the products in 59-78% yield.

X) Preparation of compound 53 (according to Scheme 5):

To a solution of N-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-benzene-1,4-diamine (0.29mmol) in CH_2Cl_2 (10mL), NEt_3 (0.29mmol) was added followed by the 5-Chloro-benzotriazole carboxamidine derivative (0.29mmol) as shown in Scheme 5. The mixture was heated at reflux for 5h. The solvent was then evaporated and the residue purified by flash chromatography to afford product BOC-protected compound as a white solid.

δ_H (d_6 DMSO): 1.50 (9H, s, Boc), 1.60 (9H, s, Boc), 4.00 (3H, s MeO), 7.15 (1H, t), 7.25 (1H, d), 7.50-7.60 (4H, m), 7.80 (2H, d), 8.05 (1H, d), 8.80 (1H, s), 9.75 (1H, s), 10.00 (1H, s) 11.55 (1H, s).

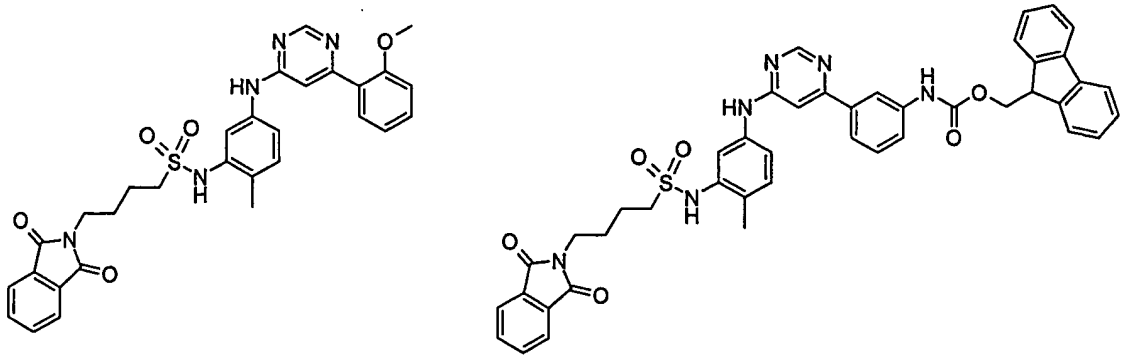
To a solution of BOC protected compound (0.11mmol) in CH_2Cl_2 (1.5mL), TFA (1.5mL) was added at room temperature and the mixture stirred at room temperature for 18h. The reaction mixture was diluted with EtOAc/H_2O (15mL, 2:1v/v) and the H_2O layer neutralised with solid $NaHCO_3$. The organic layer was then separated and the water layer extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to afford the crude product. This material was suspended in water, separated by filtration, washed with H_2O (2x), Et_2O (3x) and dried to afford product.

XIA) Preparation of compound 119 (according to Scheme 10):

2-Methyl-4-nitroaniline (1mMol) was reacted with 4,6-dichloropyrimidine (1mMol) in the presence of DIPEA (2mMol) under microwave conditions. Suzuki coupling on this substrate was performed as previously described above. Hydrogen transfer reduction was carried out following a standard protocol (S. Hanessian et al., synthesis 1981, 396). The obtained intermediate was reacted with pivaloylchlorid using the conditions as described in Scheme 2.

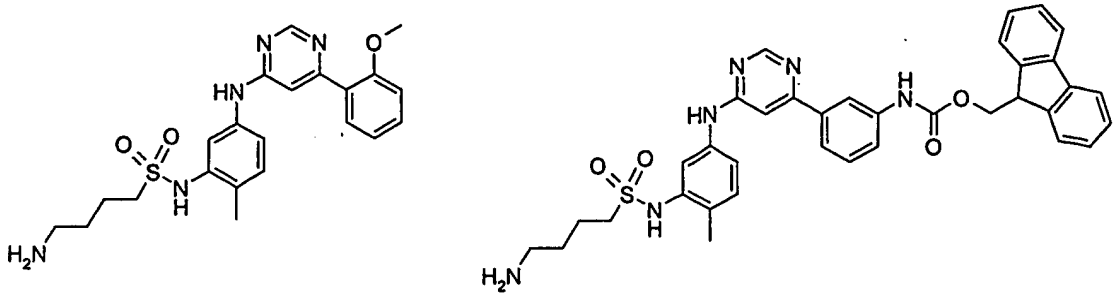
XIB) **Preparation of compound 320 and (3-{6-[3-(4-Amino-butane-1-sulfonylamino)-4-methyl-phenylamino]-pyrimidin-4-yl}-phenyl)-carbamic acid 9*H*-fluoren-9-ylmethyl ester (according to Scheme 10A):**

a) Preparation of 4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butane-1-sulfonic acid {5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-amide and [3-(6-{3-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butane-1-sulfonylamino]-4-methyl-phenylamino}-pyrimidin-4-yl)-phenyl]-carbamic acid 9*H*-fluoren-9-ylmethyl ester



Potassium 4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butane-1-sulfonate (prepared according to Jiang, J., Wang, W. Sane, D. C., and Wang, B. *Bioorg. Chem.* **2001**, *29*, 357 – 379) was converted to 4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-butane-1-sulfonyl chloride, in analogy to compounds described in the reference mentioned above. The sulfonyl chloride (0.26 mmol) and N^1-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-4-methyl-benzene-1,3-diamine (0.22 mmol; prepared according to scheme 1), or {3-[6-(3-amino-4-methyl-phenylamino)-pyrimidin-4-yl]-phenyl}-carbamic acid 9*H*-fluoren-9-ylmethyl ester (0.22 mmol; prepared according to scheme 1), were suspended in 15 ml of abs. CH_2Cl_2. Pyridine (2.2 mmol) was added, and the mixture was stirred at rt for 7 d. The solvent was evaporated under reduced pressure, and the yellow residue was taken up in DMSO (2 ml) and purified via prep.-HPLC (XTerra Prep. MS C_{18} 5 µm, 19 x 150 mm, gradient from water to MeCN over 14 min), yielding 70% of off-white powders.

b) Preparation of compound **320** and (3-{6-[3-(4-Amino-butane-1-sulfonyl-amino)-4-methyl-phenylamino]-pyrimidin-4-yl}-phenyl)-carbamic acid 9*H*-fluoren-9-ylmethyl ester



Compound 320

Any *N*-protected sulfonamide shown above (91.9 µmol) was dissolved in 10 ml of EtOH. Hydrazine monohydrate (3.7 mmol) was added, and the mixture was stirred at rt for 6 h. The solvent was evaporated under reduced pressure; the residue was re-dissolved in MeOH (3x) and the solvents evaporated. The yellow residue was taken up in DMSO (3 ml) and purified via prep.-HPLC (Zorbax Bonus-RP Prep. C_{18} 5 µm, 21.2 x 150 mm, gradient from water to MeCN over 14 min), yielding 92% of pale yellow powders.

XII) <u>Preparation of compound 120 (according to scheme 11):</u>

To a solution of 4-amino, 2-nitrophenol (1 mmol), triphenyl phosphine (1.2 mmol) and benzyl alcohol (1.2 mmol) in dry dichloromethane (5 ml) at ambient temperature, under a nitrogen atmosphere, was added a solution of diethyl azodicarboxylate (1.2 mmol) in dry dichloromethane (2 ml). The resultant mixture was stirred at ambient temperature for 18 hr. Evaporation under reduced pressure afforded a gum that was purified by column chromatography (SiO2;diethyl ether) to give 4-benzyloxy-3-nitro-aniline, yield 85%.

δ_H (d_6 DMSO): 5.24 (2H, s), 5,30 (2H, s), 6.85 – 6.95 (1H, m, ArH) 7.10 (1H, s, ArH), 7.20 (1H, d, ArH), 7.30 – 7.80 (5H, m, ArH)

The reaction of 4-benzyloxy-3-nitro-aniline with 4,6-dichloropyrimidine to afford 4-(4'benzyloxy-3-nitrophenyl)amino-*6* -chloro-pyrimidine is performed according to Preparation method 1. δ_H (d_6 DMSO): 5.34 (2H, s, CH_2Ar), 6.84, (1H, s, HetH), 7.30 –7.75 (7H, m, ArH), 8.30 (1H, m, ArH), 8.55 (1H, s, Het H), 10.10 (1H, s, NH)

To a solution of 4-(4'benzyloxy-3-nitrophenyl)amino-*6* -chloro-pyrimidine (4.91 g) and sulfuric acid (8 ml) in ethanol (300 ml) was added zinc dust (4.49 g). The mixture was then heated under reflux for 18 hours, cooled to room temperature then basified with sodium hydrogen carbonate. After evaporation under reduced pressure, the residue was dissolved in ethyl acetate and water. The organic phase was separated, washed with water, dried (MgSO4) and evaporated under reduced pressure. The residue was then subjected to column chromatography

(SiO2;ethyl acetate:petroleum ether (40/60) 1:1) to give 4-(3'-amino-4'benzyloxyphenyl)amino-6 -chloro-pyrimidine, 21% δ_H (d_6 DMSO): 4.84 (2H, s, NH_2), 5.00 (2H, s, CH_2Ph), 6.50 – 6.60 (2H, m, ArH), 6.70 – 6.80 (2H, m, ArH and HetH), 7.20 – 7.50 (5H, m, ArH), 8.30 (1H, s, HetH), 9.45 (1H, s, NH)

To a solution of 4-(3'-amino-4'benzyloxyphenyl)amino-6 -chloro-pyrimidine (630 mg) in dry dichloromethane was added pyridine (8 ml) followed by methane sulfonyl chloride (0.3 ml). The mixture was stirred at room temperature overnight then evaporated under reduced pressure. The residue was dissolved in water and dichloromethane and the organic phase separated, washed with water, dried (MgSO4) and evaporated under reduced pressure. The residue was then subjected to column chromatography (SiO2;ethyl acetate:petroleum ether (40/60) 1:1) to afford N-{5-[6-chloropyrimidin-4-ylamino]-2-benzyloxy-phenyl}-methanesulfonamide (200 mg). δ_H (d_6 DMSO): 3.14 (3H, s, SO_2Me), 5.40 (2H, s, CH_2Ph), 6.94 (1H, s, HetH), 7.30 – 7.40 (1H, m, ArH), 7.50 – 7.85 (7H, m, ArH), 8.70 (1H, s, HetH), 9.30 (1H, s, NH), 10.00 (1H, s, NH)

The reaction of N-{5-[6-chloropyrimidin-4-ylamino]-2-benzyloxy-phenyl}-methanesulfonamide with 3 aminobenzene boronic acid was performed analogously to Preparation method 2, to give
Compound 120: N-{5-[6-(3-Amino-phenyl)-pyrimidin-4-ylamino]-2-benzyloxy-phenyl}-methanesulfonamide,
δ_H (d_6 DMSO): 2.90 (3H, s, SO_2Me), 5.15, (2H, s, CH_2Ph), 5.25 (2H, s, NH_2), 6.60 – 6.70 (1H, m, ArH), 7.00 (1H, s, HetH), 7.05 – 7.15 (3H, m, ArH) 7.25 - 7.60 (8H, m, ArH), 8.55 (1H, s, HetH) 9.00 (1H, s, NH), 9.50 (1, s, NH)

XIII) Preparation of compound 103 (according to Scheme 12)

NaH (0.22mMol) was added to a solution of the pyrimidine derivative as outlined in Scheme 12 (0.22mMol) in dry DMF (2mL) under nitrogen. The solution was stirred at room temperature for 30 minutes. N-protected chloroalkyl (0.22mMol) was added and the mixture was heated at 80°C for 18 hours. The solution was allowed to cool down to room temperature. Extraction was carried out in EtOAc:H_2O. The organic phase was dried ($MgSO_4$), solvent removed in *vacuo* to give a crude product which was purified by flash column chromatography to give the desired intermediate. The intermediate was dissolved in 50% TFA solution [(2ml) in DCM plus 2 drops of H_2O] and the mixture was stirred for 18 hours at room temperature. The solvent was removed in vacuo and the residue was suspended in EtOAc. The organic phase was washed with $NaHCO_3$ (aq. sat.), the organic layer was dried ($MgSO_4$) and the solvent evaporated to give a residue which was dissolved in 1mL

of 2.5 M HCl. The solution was evaporated *in vacuo* to give a solid which was triturated with Et_2O and dried to give the desired compound as a hydrochloride salt in 23% overall yield.

Materials and Methods:

Cloning of CDK9 and Cyclin T1:

Both cDNA fragments were cloned by PCR into pDONR201 vectors using the gateway recombination system (Invitrogen) according to the manufacturer's recommendations. The fragments were subcloned into a gateway-adapted shuttle vector (pPM7) for production of recombinant adenovirus. All plasmids were verified by restriction digests and sequencing analysis.

Expression and purification of CDK9/Cyclin T1 proteins:

Expression and purification was in principle performed as described by Cotten et al. (M. Cotten et al., Nucleic acids research, 2003, 31(28), 128).

Kinase assay using CDK9/Cyclin T1:

Kinase assays were performed in principle as described by Cotten et al. (M. Cotten et al., Nucleic acids research, 2003, 31(28), 128).

Kinase assays determining CDK2/CyclinA and CDK5/p35 activity:

Kinase assays were performed as described by the manufacturers recommendations (Proqinase for CDK2/CyclinA and Upsate for CDK5/p35).

General kinase assay:

The inhibitory effect of compounds according to the present invention on the activity of protein kinases, depicted in **Table 1**, can be measured according to the following protocol:

Reaction Volume:	40µl
Reaction Time:	60min
Reaction Temperature:	room temperature
Assay Plate:	96 well U bottom plate (Greiner, 650161)
MultiScreen-PH Plate:	96 well MAPH Filter Plates (Millipore, MAPHNOB50)
Filter Washing Solution:	0.75% H_3PO_4
Szintilation Liquid:	Supermix Liquid Szintillator (PerkinElmer, 1200-439)
Controls:	
Negative Control (C-):	100mM EDTA (Ethylenediaminetetraacetic acid), no Inhibitor
Positive Control (C+):	no Inhibitor

Reaction Buffer:
20mM Tris (Tris(hydroxymethyl)aminomethane hydrochloride), pH 7.5
10mM $MgCl_2$
1mM DTT

Final Assay Concentrations:

Kinase:	Use kinase conc. yielding 10% ATP turn over.
ATP:	1 µM
Adenosine 5'-[γ-^{33}P]triphosphate:	12.5 µCi/ml (Amersham Biosciences, BF1000)
Substrate: Myelin Basic Protein	10 µM (Invitrogen, 13228-010)

Pipetting Sequence:

1) Add 10 µl 4 fold concentrated Substrate + 4 fold concentrated ATP in 3 fold concentrated Reaction Buffer to each well of Assay Plate
2) Add 10 µl 4 fold concentrated inhibitor in 4% DMSO in H_2O to each well except to C- and C+ wells
3) Add 10 µl 4% DMSO in H_2O to C- and C+ wells
4) Add 10 µl 500mM EDTA in H_2O to C- wells
5) Add 10 µl 50 µCi/ml Adenosine 5'-[γ-^{33}P]triphosphate in H_2O to each well
6) Add 10 µl 4 fold concentrated kinase in Reaction Buffer to each well
7) Incubate 1hr at room temperature
8) Add 10 µl 50mM EDTA in H_2O to each well except to C- wells
9) Prepare MAPH plates by adding 200 µl 0.75% H_3PO_4 to each well
10) Exhaust 0.75% H_3PO_4 using Millipore vacuum station
11) Add 60 µl 0.75% H_3PO_4 to each well of MAPH Filter Plate
12) Transfer 30 µl sample per well from Assay Plate to corresponding well of MAPH Filter Plate
13) Incubate 30 min at room temperature
14) Wash each well of MAPH Filter Plates 3x with 200 µl 0.75% H_3PO_4 using Millipore vacuum station.
15) Add 20 µl Szintilation Liquid to each well of MAPH Filter Plate
16) Seal MAPH Filter Plate
17) Store MAPH Filter Plate 30 min in darkness
18) Quantify radioactivity

Table 1: List of all protein kinases

No.	Accession Number	Gene
1	NM_001105	ACVR1 (activin A receptor, type I)
2	NM_004302	ACVR1B (activin A receptor, type IB)
3	NM_145259	ACVR1C, ALK7
4	NM_001616	ACVR2, activin A receptor, type II
5	NM_001106	ACVR2B, activin A receptor, type IIB
6	NM_000020	ACVRL1 (activin A receptor type II-like 1)
7	NM_004612	TGFBR1 (transforming growth factor, beta receptor I (activin A receptor type II-like kinase, 53kD))
8	NM_003242	TGFBR2 (transforming growth factor, beta receptor II)
9	NM_004329	BMPR1A (bone morphogenetic protein receptor, type IA)
10	NM_001203	BMPR1B (bone morphogenetic protein receptor, type IB)
11	NM_001204	BMPR2 (bone morphogenetic protein receptor, type II (serine/threonine kinase))
12	NM_006251	PRKAA1 (protein kinase, AMP-activated, alpha 1 catalytic subunit)
13	NM_006252	PRKAA2 (protein kinase, AMP-activated, alpha 2 catalytic subunit)
14	NM_002929	GRK1; rhodopsin kinase
15	NM_001619	GRK2
16	NM_005160	GRK3
17	NM_005307	GRK4
18	NM_005308	GRK5
19	NM_002082	GRK6
20	NM_139209	GRK7 (G protein-coupled receptor kinase 7)
21	NM_017572	MKNK2, GPRK7
22	NM_001654	ARAF1 (v-raf murine sarcoma 3611 viral oncogene homolog 1)
23	NM_004333	BRAF (v-raf murine sarcoma viral oncogene homolog B1)
24	NM_002880	RAF1 (v-raf-1 murine leukemia viral oncogene homolog 1)
25	NM_021574	BCR1
26	NM_003656	CAMK1 (calcium/calmodulin-dependent protein kinase I)
27	NM_015981	CAMK2A (calcium/calmodulin-dependent protein kinase (CaM kinase) II alpha)
28	NM_001220	CAMK2B (calcium/calmodulin-dependent protein kinase (CaM kinase) II beta)
29	NM_001221	CAMK2D (calcium/calmodulin-dependent protein kinase (CaM kinase) II delta)
30	NM_020439	CAMK1G (calcium/calmodulin-dependent protein kinase IG)
31	NM_001222	CAMK2G (calcium/calmodulin-dependent protein kinase (CaM kinase) II gamma)
32	NM_001744	CAMK4 (calcium/calmodulin-dependent protein kinase IV)
33	NM_001786	CDC2 (cell division cycle 2)
34	NM_001798	CDK2 (cyclin-dependent kinase 2)
35	NM_001258	CDK3 (cyclin-dependent kinase 3)
36	NM_000075	CDK4 (cyclin-dependent kinase 4)
37	NM_004935	CDK5 (cyclin-dependent kinase 5)
38	NM_001259	CDK6 (cyclin-dependent kinase 6)
39	NM_001799	CDK7 (cyclin-dependent kinase 7)
40	NM_001260	CDK8 (cyclin-dependent kinase 8)
41	NM_001261	CDK9 (cyclin-dependent kinase 9 (CDC2-related kinase))
42	NM_003674	CDK10 (cyclin-dependent kinase (CDC2-like) 10)
43	NM_015076	CDK11, DPK
44	NM_004196	CDKL1 (cyclin-dependent kinase-like 1); KKIALRE
45	NM_003948	CDKL2 (cyclin-dependent kinase-like 2); KKIAMRE
46	NM_016508	CDKL3 (cyclin-dependent kinase-like 3); NKIAMRE
47	XM_293029	CDKL4, similar to cyclin-dependent kinase-like 1
48	NM_033489	CDC2L1 (cell division cycle 2-like 1); PITSLRE B
49	NM_024011	CDC2L1 (cell division cycle 2-like 1); PITSLRE A
50	NM_003718	CDC2L5 (cell division cycle 2-like 5)
51	NM_006201	PCTK1 (PCTAIRE protein kinase 1)
52	NM_002595	PCTK2 (PCTAIRE protein kinase 2)
53	NM_002596	PCTK3 (PCTAIRE protein kinase 3)
54	NM_012395	PFTK1 (PFTAIRE protein kinase 1)
55	NM_001278	IKK-alpha; CHUK
56	NM_001556	IKK-beta; IKK2

No.	Accession Number	Gene
57	NM_001892	CSNK1A1 (casein kinase 1, alpha 1)
58	NM_001893	CSNK1D (casein kinase 1, delta)
59	NM_001894	CSNK1E (casein kinase 1, epsilon)
60	NM_004384	CSNK1G3 (casein kinase 1, gamma 3)
61	NM_001319	CSNK1G2 (casein kinase 1, gamma 2)
62	NM_001895	CSNK2A1 (casein kinase 2, alpha 1)
63	NM_001896	CSNK2A2 (casein kinase 2, alpha prime)
64	NM_022048	CSNK1G1 (casein kinase 1, gamma 1)
65	NM_004071	CLK1 (CDC-like kinase 1)
66	NM_003993	CLK2 (CDC-like kinase 2)
67	NM_003992	CLK3 (CDC-like kinase 3)
68	NM_020666	CLK4 (CDC-like kinase 4)
69	NM_004938	DAPK1 (death-associated protein kinase 1)
70	NM_014326	DAPK2 (death-associated protein kinase 2)
71	NM_001348	DAPK3 (death-associated protein kinase 3)
72	NM_004954	EMK1 (ELKL motif kinase)
73	NM_002746	MAPK3; ERK1
74	NM_002745	MAPK1, ERK2
75	NM_002748	MAPK6; ERK3
76	NM_002747	MAPK4; ERK3-related
77	NM_002749	MAPK7; ERK5
78	NM_001315	MAPK14; CSBP1
79	NM_002751	MAPK11; p38beta
80	NM_002969	MAPK12; ERK6, p38g
81	NM_002754	MAPK13; p38delta
82	AY065978	ERK8
83	NM_002750	MAPK8; JNK1
84	NM_002752	MAPK9; JNK2
85	NM_002753	MAPK10; JNK3
86	NM_006712	FASTK (Fas-activated protein kinase)
87	NM_004579	MAP4K2; GCK

No.	Accession Number	Gene
88	NM_019884	GSK3A (glycogen synthase kinase 3 alpha)
89	NM_002093	GSK3B (glycogen synthase kinase 3 beta)
90	NM_002576	PAK1
91	NM_002577	PAK2
92	NM_002578	PAK3
93	NM_005884	PAK4
94	NM_020341	PAK5 (PAK7)
95	NM_020168	PAK6
96	NM_007181	MAP4K1; HPK1
97	NM_004517	ILK (integrin-linked kinase)
98	NM_001569	IRAK1 (interleukin-1 receptor-associated kinase 1)
99	NM_001570	IRAK2 (interleukin-1 receptor-associated kinase 2)
100	NM_007199	IRAK-M
101	NM_016123	IRAK4
102	NM_006575	MAP4K5
103	NM_002314	LIMK1 (LIM domain kinase 1)
104	NM_005569	LIMK2 (LIM domain kinase 2)
105	NM_000455	STK11; LKB1
106	NM_005906	MAK (male germ cell-associated kinase)
107	NM_002755	MAP2K1; MEK1
108	NM_030662	MAP2K2; MEK2
109	NM_002756	MAP2K3; MEK3
110	NM_003010	MAP2K4; MEK4
111	NM_002757	MAP2K5; MEK5
112	NM_002758	MAP2K6; MEK6
113	NM_005043	MAP2K7; MKK7
114	XM_042066	MAP3K1; MEKK1
115	NM_006609	MAP3K2; MEKK2
116	NM_002401	MAP3K3; MEKK3
117	NM_005922	MAP3K4; MEKK4
118	NM_005923	MAP3K5; ASK1

No.	Accession Number	Gene
119	NM_004672	MAP3K6
120	NM_003188	MAP3K7; TAK1
121	NM_005204	MAP3K8; Tpl-2
122	XM_027237	MAP3K9; MLK1
123	NM_002446	MAP3K10; MST; MLK2
124	NM_002419	MAP3K11; MLK3
125	NM_006301	MAP3K12; DLK
126	NM_004721	MAP3K13; LZK
127	NM_003954	MAP3K14; NIK
128	AX282911	MAP3K7, similar to MAP/ERK kinase kinase 5; apoptosis signal regulating kinase
129	AX504239	MAP3K8
130	NM_015112	MAST205
131	NM_005965	MYLK (myosin, light polypeptide kinase)
132	NM_033118	MYLK2 (myosin light chain kinase 2)
133	NM_005372	MOS (v-mos Moloney murine sarcoma viral oncogene homolog)
134	NM_006282	STK4; MST1
135	NM_006281	STK3; MST2
136	NM_003576	STK24; MST3
137	NM_012224	NEK1 (NIMA (never in mitosis gene a)-related kinase 1)
138	NM_002497	NEK2 (NIMA (never in mitosis gene a)-related kinase 2)
139	NM_002498	NEK3 (NIMA (never in mitosis gene a)-related kinase 3)
140	AX394707	NEK5
141	NM_014397	NEK6 (NIMA (never in mitosis gene a)-related kinase 6)
142	NM_133494	NEK7
143	NM_178170	NEK8, NEK12A
144	NM_033116	NEK9
145	AX250157	NEK10
146	NM_024800	NEK11
147	NM_003157	STK2
148	NM_005406	ROCK1 (Rho-associated, coiled-coil containing protein kinase 1); p160ROCK
149	NM_004850	ROCK2 (Rho-associated, coiled-coil containing protein kinase 2)
150	NM_007271	STK38; NDR
151	NM_015000	STK38L, NDR2
152	NM_004409	DMPK1 (dystrophia myotonica-protein kinase)
153	XM_290516	DMPK2, HSMDPKIN
154	NM_003607	MRCKalpha (PK428)
155	NM_007174	Citron
156	NM_002613	PDPK1 (3-phosphoinositide dependent protein kinase-1)
157	NM_006213	PHKG1 (phosphorylase kinase, gamma 1)
158	NM_000294	PHKG2 (phosphorylase kinase, gamma 2)
159	NM_002648	PIM1
160	NM_006875	PIM2
161	AR208686	PIM3
162	NM_014791	KIAA0175
163	NM_002730	PRKACA (protein kinase, cAMP-dependent, alpha)
164	NM_002731	PRKACB (protein kinase, cAMP-dependent, beta)
165	NM_002732	PRKACG (protein kinase, cAMP-dependent, gamma)
166	NM_002742	PRKCM (protein kinase C, mu)
167	NM_002737	PRKCA (protein kinase C, alpha)
168	NM_002738	PRKCB1 (protein kinase C, beta 1)
169	NM_006254	PRKCD (protein kinase C, delta)
170	NM_005400	PRKCE (protein kinase C, epsilon)
171	NM_002739	PRKCG (protein kinase C, gamma)
172	NM_006255	PRKCH (protein kinase C, eta)
173	NM_002740	PRKCI (protein kinase C, iota)
174	NM_006257	PRKCQ (protein kinase C, theta)
175	NM_002744	PRKCZ (protein kinase C, zeta)
176	NM_002741	PRKCL1 (protein kinase C-like 1)
177	NM_006256	PRKCL2 (protein kinase C-like 2)
178	NM_006258	PRKG1 (protein kinase, cGMP-dependent, type I)
179	NM_006259	PRKG2 (protein kinase, cGMP-dependent, type II); cGKII

No.	Accession Number	Gene
180	NM_002759	PRKR (protein kinase, interferon-inducible double stranded RNA dependent)
181	NM_006852	TLK2 (tousled-like kinase 2)
182	NM_012290	TLK1 (tousled-like kinase 1)
183	NM_005044	PRKX (protein kinase, X-linked)
184	NM_005030	PLK (polo-like kinase)
185	NM_004073	CNK (cytokine-inducible kinase)
186	NM_003913	PRPF4B
187	NM_006742	PSKH1 (protein serine kinase H1)
188	NM_005163	AKT1 (v-akt murine thymoma viral oncogene homolog 1)
189	NM_001626	AKT2 (v-akt murine thymoma viral oncogene homolog 2)
190	NM_005465	AKT3 (v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma))
191	NM_014264	STK18; Sak
192	NM_005627	SGK (serum/glucocorticoid regulated kinase)
193	NM_002376	MARK3 (MAP/microtubule affinity-regulating kinase 3)
194	NM_006374	STK25; YSK1
195	NM_003137	SRPK1 (SFRS protein kinase 1)
196	NM_182692	SRPK2 (SFRS protein kinase 2)
197	NM_003319	Titin
198	NM_003318	TTK protein kinase
199	NM_003384	VRK1 (vaccinia related kinase 1)
200	NM_006296	VRK2 (vaccinia related kinase 2)
201	NM_003390	WEE1
202	NM_018650	MARK1 (MAP/microtubule affinity-regulating kinase 1)
203	NM_003160	STK13; (aurora/IPL1-like), AIE2, aurora kinase C
204	NM_004759	MAPKAPK2
205	NM_004635	MAPKAPK3
206	NM_003668	MAPKAPK5
207	NM_005734	HIPK3 (homeodomain interacting protein kinase 3), DYRK6
208	NM_003503	CDC7L1 (CDC7 cell division cycle 7-like 1)
209	NM_016231	NLK

No.	Accession Number	Gene
210	NM_003565	ULK1 (unc-51-like kinase 1)
211	NM_014683	ULK2 (unc-51-like kinase 2)
212	AX056454	DKFZP434C131 protein, ULK3
213	NM_017886	hypothetical protein FLJ20574, ULK4
214	NM_053006	STK22B; TSSK2
215	NM_003684	MKNK1 (MAP kinase-interacting serine/threonine kinase 1); MNK1
216	NM_003804	RIPK1 (receptor (TNFRSF)-interacting serine-threonine kinase 1); RIP
217	NM_003821	RIPK2 (receptor-interacting serine-threonine kinase 2); RICK
218	NM_006871	RIPK3 (receptor-interacting serine-threonine kinase 3); RIP3
219	NM_003600	STK6; BTAK, AIK
220	NM_004217	STK12; IPL1, aurora kinase B
221	NM_006549	CAMKK2 (calcium/calmodulin-dependent protein kinase kinase 2, beta)
222	NM_017719	SNRK (SNF-1 related kinase)
223	NM_001433	ERN1 (ER to nucleus signalling 1)
224	NM_004336	BUB1 (BUB1 budding uninhibited by benzimidazoles 1 homolog)
225	NM_001211	BUB1B (BUB1 budding uninhibited by benzimidazoles 1 homolog beta)
226	NM_006622	SNK (serum-inducible kinase)
227	NM_001274	CHEK1 (CHK1 checkpoint homolog)
228	NM_003957	STK29; PEN11B
229	NM_013233	STK39; SPAK
230	NM_003691	STK16; PKL12
231	XM_290796	TAO1/KIAA1361
232	NM_003159	STK9
233	NM_014586	HUNK (hormonally upregulated Neu-associated kinase)
234	NM_004834	MAP4K4; NIK; HGK
235	NM_002953	RPS6KA1 = ribosomal protein S6 kinase, 90kD, polypeptide 1
236	NM_021135	RPS6KA2 (ribosomal protein S6 kinase, 90kD, polypeptide 2); RSK3
237	NM_003161	RPS6KB1 (ribosomal protein S6 kinase, 70kD, polypeptide 1)
238	NM_004586	RPS6KA3 = ribosomal protein S6 kinase, 90kD, polypeptide 3; RSK2
239	NM_004755	RPS6KA5 (ribosomal protein S6 kinase, 90kD, polypeptide 5); MSK1
240	NM_003942	RPS6KA4 (ribosomal protein S6 kinase, 90kD, polypeptide 4); MSK2

No.	Accession Number	Gene
241	NM_003952	RPS6KB2 (ribosomal protein S6 kinase, 70kD, polypeptide 2)
242	NM_004760	STK17A; DRAK1
243	NM_014413	HRI (heme-regulated initiation factor 2-alpha kinase)
244	NM_007194	CHEK2 (CHK2 checkpoint homolog)
245	NM_012119	CCRK (cell cycle related kinase)
246	NM_014370	STK23; MSSK1
247	NM_005990	STK10; LOK
248	NM_004836	EIF2AK3 (eukaryotic translation initiation factor 2-alpha kinase 3)
249	NM_003618	MAP4K3; GLK
250	NM_014720	SLK (SNF1 sucrose nonfermenting like kinase)
251	NM_014602	PIK3R4 (phosphoinositide-3-kinase, regulatory subunit 4, p150)
252	NM_006285	TESK1 (testis-specific kinase 1)
253	NM_021643	GS3955 protein
254	NM_004203	PKMYT1
255	NM_015148	PASK (PAS domain containing serine/threonine kinase)
256	NM_014002	IKKE (IKK-related kinase epsilon; inducible IkappaB kinase)
257	NM_007118	TRIO (triple functional domain (PTPRF interacting))
258	NM_001396	DYRK1A (dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A)
259	NM_004714	DYRK1B (dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1B)
260	NM_003583	DYRK2 (dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 2)
261	NM_003582	DYRK3 (dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 3)
262	NM_003845	DYRK4 (dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 4)
263	NM_031417	MARKL1 (MAP/microtubule affinity-regulating kinase like 1)
264	NM_014840	KIAA0537 gene product
265	XM_039796	TNIK (Traf2 and NCK interacting kinase)
266	XM_038150	MAST3, KIAA0561 protein
267	XM_291141	MAST4, KIAA0303 protein
268	NM_015375	DustyPK
269	NM_002760	PRKY (protein kinase, Y-linked)
270	NM_003688	CASK (calcium/calmodulin-dependent serine protein kinase (MAGUK family))
271	NM_004734	DCAMKL1 (doublecortin and CaM kinase-like 1)
272	NM_152619	hypothetical protein MGC45428, DCAMKL2
273	AX504237	DCAMKL3, KIAA1765 protein
274	NM_004226	STK17B; DRAK2
275	NM_005813	PRKCN (protein kinase C, nu)
276	NM_005255	GAK (cyclin G associated kinase)
277	NM_032294	hypothetical protein DKFZp761M0423
278	NM_014226	RAGE1 (renal tumor antigen)
279	NM_006035	CDC42BPB (CDC42 binding protein kinase beta (DMPK-like))
280	NM_007170	TESK2 (testis-specific kinase 2)
281	NM_152696	Nbak2, KIAA0630 protein
282	NM_016151	PSK
283	NM_173354	SNF1LK, SIK
284	AB023190	SAST (syntrophin associated serine/threonine kinase)
285	NM_022740	HIPK2 (homeodomain interacting protein kinase 2)
286	AX236110	GCN2, eIF2alpha kinase
287	NM_013355	PKNbeta
288	NM_198465	NRK/ZC4 (NIK-related kinase)
289	NM_013257	SGKL (serum/glucocorticoid regulated kinase-like)
290	NM_016276	SGK2 (serum/glucocorticoid regulated kinase 2)
291	NM_012424	RPS6KC1 (ribosomal protein S6 kinase, 52kD, polypeptide 1)
292	NM_014496	RPS6KA6 (ribosomal protein S6 kinase, 90kD, polypeptide 6); RSK4
293	NM_013254	TBK1 (TANK-binding kinase 1)
294	NM_016281	JIK
295	NM_016440	VRK3 for vaccinia related kinase 3
296	NM_015716	MINK (Misshapen/NIK-related kinase)
297	AX166520	similar to Ca2+/Calmodulin-dependent protein kinase I, CAMK1b
298	NM_006410	HTATIP2 (HIV-1 Tat interactive protein 2, 30 kD)
299	NM_016542	MST4

No.	Accession Number	Gene
300	NM_016653	ZAK (sterile-alpha motif and leucine zipper containing kinase AZK)
301	NM_173575	PKE, YANK3
302	NM_018979	PRKWNK1 (protein kinase, lysine deficient 1); WNK1
303	NM_006648	PRKWNK2 (protein kinase, lysine deficient 2)
304	NM_020922	PRKWNK3 (protein kinase, lysine deficient 3)
305	NM_032387	PRKWNK4 (protein kinase, lysine deficient 4)
306	NM_018492	TOPK (T-LAK cell-originated protein kinase)
307	AL359916 (longer at 5')	STK35, CLIK1
308	NM_020680	NTKL (N-terminal kinase-like)
309	NM_032844	MASTL, hypothetical protein FLJ14813
310	NM_020397	CKLiK, CamKI-like protein kinase
311	AX224725	SCYL2
312	NM_153335	STLK5, LYK5
313	NM_174944	TSSK4
314	NM_052841	STK22C; TSSK3
315	XM_166453	TTBK1
316	AR004796	KSR1 (kinase suppressor of ras)
317	NM_032037	SSTK
318	NM_016457	PKD2 (polycystic kidney disease 2)
319	NM_025195	C8FW, Trb1
320	NM_033266	ERN2 (ER to nucleus signalling 2)
321	NM_020423	PACE-1
322	NM_033550	PRPK
323	NM_018401	serine/thronine kinase HSA250839, YANK2
324	NM_020639	ANKRD3 (ankyrin repeat domain 3); DIK
325	NM_015690	STK36
326	NM_014572	LATS2 (LATS, large tumor suppressor, homolog 2)
327	AX056397	SPEG, KIAA1297 protein
328	AX504253	Wee1B
329	AX766335	QSK, KIAA0999 protein

No.	Accession Number	Gene
330	NM_007064	TRAD
331	NM_004690	LATS1 (LATS, large tumor suppressor, homolog 1)
332	NM_014911	AAK1
333	NM_014920	ICK, MAK-related kinase
334	NM_198892	BMP2K, BIKE
335	NM_033126	PSKH2
336	NM_031464	hypothetical protein MGC11287 similar to ribosomal protein S6 kinase
337	NM_032409	PINK1 (PTEN induced putative protein kinase 1)
338	NM_013392	NRBP (nuclear receptor binding protein
339	NM_016507	CrkRS
340	NM_005109	OSR1 (oxidative-stress responsive 1)
341	NM_139158	ALS2CR7
342	NM_032028	STK22D, TSSK1
343	NM_017771	PXK (PX domain-containing protein kinase), Slob
344	NM_018571	ALS2CR2 (amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 2), STLK6
345	NM_031965	GSG2, haspin
346	NM_015191	SIK2, QIK
347	AX039412	KIAA1639, Obscn
348	AX207388	YANK1
349	AX394712	similar to MLCK, hypothetical protein LOC340156
350	NM_178510	ANKK1
351	NM_021158	C20orf97 (chromosome 20 open reading frame 97), Trb3
352	NM_152649	MLKL, hypothetical protein FLJ34389
353	AX250159	SgK223, DKFZp761P0423
354	XM_370878	KIAA2002
355	NM_024652	LRRK1
356	NM_033115	TBCK, hypothetical portein MGC16169
357	AX250163	SgK424, similar to testis expressed gene 14 (LOC126392)
358	NM_031272	TEX14 (testis expressed sequence 14)
359	NM_024046	hypothetical protein MGC8407, VACAMKL

No.	Accession Number	Gene
360	NM_014916	LMTK2, KIAA1079 protein, LMR2, KPI-2
361	NM_017433	MYO3A
362	NM_138995	MYO3B
363	NM_030952	SNARK
364	NM_030906	STK33
365	NM_182493	similar to myosin light chain kinase (MLCK)
366	NM_032430	BRSK1, KIAA1811
367	XM_370948	SBK, similar to SH3-binding kinase (LOC388228)
368	NM_032017	SINK-homologous serine/threonine kinase, MGC4796
369	NM_020547	AMHR2 (anti-Mullerian hormone receptor, type II)
370	NM_031414	STK31
371	NM_032237	hypothetical protein FLJ23356
372	NM_021133	RNASEL (ribonuclease L (2',5'-oligoisoadenylate synthetase-dependent))
373	AX166516	similar to protein kinase Bsk146
374	NM_153361	NIM1, MGC42105, similar to serine/threonine kinase (KIN1/SNF1/Nim1 subfamily)
375	NM_145203	casein kinase 1 alpha S-like, CKIa2
376	NM_173500	TTBK2
377	NM_144685	HIPK4
378	NM_175866	KIS
379	AX166547	KSR2
380	AX056416	NRBP2
381	AX540378	SgK494, hypothetical protein FLJ25006
382	NM_152835	CLIK1L
383	AX540373	SgK071, similar to MGC43306 protein (LOC401568)
384	AX056460	SgK493, hypothetical protein BC007901 (LOC91461)
385	NM_005157	ABL1
386	NM_005158	ABL2, ARG
387	NM_005781	ACK1
388	NM_000061	BTK
389	NM_005246	FER
390	NM_002005	FES
391	NM_002031	FRK (fyn-related kinase)
392	NM_002037	FYN
393	NM_002110	HCK
394	NM_005248	FGR
395	NM_005356	LCK
396	NM_002344	LTK
397	NM_002350	LYN
398	NM_004383	CSK
399	NM_005546	ITK
400	NM_005417	SRC
401	NM_003215	TEC
402	NM_005433	YES
403	NM_003328	TXK
404	NM_080823	SRMS
405	NM_001715	BLK
406	NM_001721	BMX
407	NM_005975	PTK6
408	NM_002821	PTK7
409	NM_002822	PTK9
410	NM_007284	PTK9L
411	NM_000222	KIT
412	NM_005211	CSF1R
413	NM_005232	EphA1
414	NM_004431	EphA2
415	NM_005233	EphA3
416	NM_004438	EphA4
417	NM_004439	EphA5
418	AX250164	EphA6
419	NM_004440	EphA7

No.	Accession Number	Gene
420	NM_020526	EphA8
421	AX166562	EphA10
422	NM_004441	EphB1
423	NM_004442	EphB2
424	NM_004443	EphB3
425	NM_004444	EphB4
426	NM_004445	EphB6
427	NM_000604	FGFR1
428	NM_000141	FGFR2
429	NM_000142	FGFR3
430	NM_002011	FGFR4
431	NM_002253	KDR
432	NM_002019	FLT1
433	NM_004119	FLT3
434	NM_002020	FLT4
435	NM_005228	EGFR
436	NM_004448	HER2
437	NM_001982	HER3
438	NM_005235	HER4
439	NM_002378	MATK
440	NM_000875	IGF1R
441	NM_000208	INSR
442	NM_014215	INSRR
443	NM_002227	JAK1
444	NM_004972	JAK2
445	NM_000215	JAK3
446	NM_003331	TYK2
447	NM_006343	MER
448	NM_021913	AXL
449	NM_006293	TYRO3
450	NM_000245	MET

No.	Accession Number	Gene
451	NM_002447	MST1R, RON
452	NM_002958	RYK
453	NM_006206	PDGFRalpha
454	NM_002609	PDGFRbeta
455	NM_020630	RET
456	NM_005012	ROR1
457	NM_004560	ROR2
458	NM_002944	ROS1
459	NM_005607	PTK2, FAK
460	NM_004103	PTK2B, PYK2
461	NM_003177	SYK
462	NM_001079	ZAP70
463	NM_005424	TIE1
464	NM_000459	TEK, TIE2
465	NM_005592	MUSK
466	NM_002529	NTRK1
467	NM_006180	NTRK2
468	NM_002530	NTRK3
469	NM_013994	DDR1
470	NM_006182	DDR2
471	NM_004920	AATK/LMR1
472	XM_055866	LMTK3
473	NM_003985	TNK1
474	L08961	HUMSPRMTK
475	NM_004304	ALK
476	NM_015978	CARK
477	NM_018423	DKFZp761P1010
478	NM_032435	KIAA1804, MLK4
479	AJ277481	ILK-2
480	NM_000906	NPR1
481	NM_000907	NPR2

No.	Accession Number	Gene
482	NM_004963	GUCY2C
483	NM_000180	GUCY2D
484	NM_001522	GUCY2F
485	XM_058513	DKFZp434H2111
486	NM_006218	PIK3CA (phosphoinositide-3-kinase, catalytic, alpha polypeptide)
487	NM_006219	PIK3CB (phosphoinositide-3-kinase, catalytic, beta polypeptide)
488	NM_002649	PIK3CG (phosphoinositide-3-kinase, catalytic, gamma polypeptide)
489	NM_005026	PIK3CD (phosphoinositide-3-kinase, catalytic, delta polypeptide
490	NM_014006	SMG1
491	NM_000051	ATM (ataxia telangiectasia mutated)
492	NM_001184	ATR (ataxia telangiectasia and Rad3 related)
493	NM_014216	ITPK1
494	NM_004958	FRAP1 (FK506 binding protein 12-rapamycin associated protein 1)
495	NM_002645	PIK3C2A (phosphoinositide-3-kinase, class 2, alpha polypeptide)
496	NM_002647	PIK3C3 (phosphoinositide-3-kinase, class 3); Vps34
497	NM_002651	PIK4CB (phosphatidylinositol 4-kinase, catalytic, beta polypeptide)
498	NM_002650	PIK4CA (phosphatidylinositol 4-kinase, catalytic, alpha polypeptide)
499	NM_003496	TRRAP (transformation/transcription domain-associated protein)
500	NM_002646	PIK3C2B (phosphoinositide-3-kinase, class 2, beta polypeptide)
501	NM_004570	PIK3C2G (phosphoinositide-3-kinase, class 2, gamma polypeptide)
502	NM_006904	PRKDC (protein kinase, DNA-activated)
503	NM_013302	elongation factor-2 kinase
504	NM_025144	LAK (lymphocyte alpha-kinase)
505	NM_017662	TRPM6
506	NM_052947	HAK
507	NM_020778	MIDORI
508	NM_005881	BCKDK
509	NM_002610	PDK1
510	NM_002611	PDK2
511	NM_005391	PDK3
512	NM_002612	PDK4
513	NM_018343	RIOK2
514	NM_031480	RIOK1
515	NM_003831	RIOK3
516	BC017459	ADCK1
517	NM_052853	ADCK2
518	NM_020247	CABC1
519	NM_024876	ADCK4
520	NM_174922	ADCK5
521	NM_032454	STK19
522	NM_001726	BRDT
523	NM_005104	BRD2
524	NM_007371	BRD3
525	NM_058243	BRD4, var. long
526	NM_014299	BRD4, var. Short
527	NM_004606	TAF1
528	NM_153809	TAF1L
529	NM_003852	TIF1
530	NM_005762	TRIM28
531	NM_015906	TRIM33

Accession Numbers were obtained from the public data bank NCBI (http://www.ncbi.nlm.nih.gov/).

Determination of RNA Polymerase II C-terminal domain phosphorylation:

The phosphorylation status of RNA polymerase II C-terminal domain was determined by western blot techniques. PM1 cells were seeded in 6-well plates at a density of $5x10^5$ per well. After over night incubation cells were treated with compound as indicated in the respective experiments. Cells were pelleted and lysed with 300µL 3x Laemmli buffer followed by 30min denaturing at 65°C. After separation of equal lysate volumes by SDS-PAGE the proteins were transferred to nitrocellulose membranes (Schleicher&Schuell) and probed with anti-SER2 (H5), anti-SER5 (H14) or RNA Poll II-antibodies purchased from Eurogentec and Santa Cruz, respectively. The amount of reactive protein was visualized by ECL detection methods (Amersham).

Growth assay using Alamar Blue™:

PM1 cells were seeded in 12-well plates at a density of $1.5x10^5$ per well with RPMI 1640 containing 10% FCS (fetal calf serum), 1% L-Glutamine and 1% Na-Pyruvate (Sigma). Cells were incubated with compound for 2-3 days (37°C, 6% CO_2) followed by subsequent splitting and renewing of compound-containing medium. At each of these time points an aliquot of cells served as data point for relative growth (given in % of the DMSO control [= 100%]). The cell number was determined by addition of 10µL Alamar Blue™ (Biozol) to 100µL cell aliquots following the manufacturer's instructions.

HIV replication assay in PM1 cells:

PM1 cells were seeded in 12-well plates at a density of $1.5x10^5$ per well with RPMI 1640 containing 10% FCS, 1% L-Glutamine and 1% Na-Pyruvate (Sigma). Cells were previously infected with HIV-1 BaL for 3h at a concentration of about $5x10^8$ µg p24/cell. After addition of the respective compounds cells were incubated for 6 to 10 days. During this incubation the cells were passaged and compound-containing medium was renewed. The concentration of p24 in the cellular supernatants was determined at each of this time points using a previously described ELISA assay (Bevec et al., Proceedings of the National Academy of Sciences U.S.A. 1992, 89(20), 9870 - 9874).

NFκB-dependent transcriptional activity:

The used NIH 3T3 75E11/300D8 cell line is described elsewhere (J. Eickhoff et al., Journal of Biological Chemistry, 2004, 279(10), 9642 - 9652).

HBV-replication:

To test anti-HBV-activity of compounds the HBV-producing cell line HepG2-2.2.15 (M.A. Sells, PNAS 1987, 84, 1005-1009) was used. $1.0x10^4$cells were seeded in 96-well microtiter plates in DMEM medium supplemented with 10% FCS. After incubation at 37°C in 5%CO_2 atmosphere for 24 hours the medium was replaced with fresh medium containing the appropriately diluted compound. 3 days later medium was replaced by freshly prepared inhibitor-containing medium and the cells were incubated for further 3 days. Subsequently 200µl lysis buffer (50mM Tris-Cl 7.5; 1mM EDTA 8.0; 0.5% NP40) per well was added. To remove cell debris and nucleic acids, lysate was centrifuged (15000rpm, 10min, 4°C). Cellular and viral RNA was removed by addition of 2µl of RNase. 100µl of the samples were spotted onto an uncharged nylon membrane pre-wetted with PBS (phosphate-buffered saline) using a 96well-blotting chamber (MINIfold Dot-Blot, Schleicher&Schüll). After further washing with 200µl PBS per well the membrane was treated twice with 0.5M NaOH, 1.5M NaCl (2min) and 4 times with 0.5M Tris 7.5, 3M NaCl (1min). The nucleic acids were fixed by UV-treatment and used for hybridisation with a radioactive HBV-fragment prepared from the overgenome-length HBV- plasmid pT-HBV1.3 (L.G. Guidotti et al., Journal of Virology 1995., 69(10), 6158 – 6169).

The fixed membrane was pre-hybridized in a standard hybridisation buffer (50% formamide, 5xSSPE, 10xDenhards, 1% SDS, 100µg/ml salmon sperm DNA) for at least 3 hours at 42°C and hybridised overnight against the labelled HBV-fragment. The preparation of the HBV-fragment with the "Random primers DNA labelling system" (Invitrogen) was done according to the manufacturer's instructions. Hybridized filter were washed at room temperature with 2xSSC, at 62°C with 2xSSC, 0.5%SDS and at 62°C with 0.5xSSC, 0.5%SDS. Each washing step was carried out twice. The intensity of the HBV-DNA was quantified using a phosphoimager (Fuji). To test the cell viability $0.5x10^4$ HepG2-2.2.15-cells were seeded in 96-well-microtiter plates in DMEM medium supplemented with 10% fetal bovine serum. After incubation at 37°C for 24 hours the medium was replaced by fresh compound-containing medium. 3 days later medium was replaced again by freshly prepared medium containing the inhibitor and the cells were incubated for further 3 days at 37°C. After the incubation period 1/10 volume of Alamar Blue (Serotec) solution containing a growth dependant indicator was added and the cells were incubated for 3 h at 37°C. Absorbance was monitored at 570nm and 600nm wavelength.

HCMV replication:

Human foreskin fibroblasts (HFF) cell culture were grown in DMEM containing 10% FCS.For HCMV-replication assays, HFF cells were infected with HCMV strain AD169 producing EGFP (HCMV AD169-GFP; 27). 1h post infection, medium was changed with medium containing the indicated compound concentration (0.3 μM, 1μM and 3μM, respectively) After incubation of 7days cells were lysed (in 25mM Tris, pH 7.5, 2mM DTT, 1% Triton X-100 and 10% glycerol) and analysed for EGFP content in a Wallac Victor fluorescence detector.

HCV replicon assays:

Compounds were tested for activity in the HCV replicon system described by Bartenschlager and coworkers (Lohmann et al, Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. Science 285, 110. 1999).

Affinity chromatography experiments:

Compound immobilisation:

Coupling to epoxy-groups: 500μl drained epoxy-activated Sepharose 6B (Amersham Biosciences) equilibrated to 50% DMF/0.1M Na_2CO_3 were resuspended in 1ml 20mM Compound 102 or 20mM Compound 103, respectively, dissolved in 50% DMF (Dimethylfomamid)/0.1M Na_2CO_3. 5μl 10M NaOH was added followed by in-cubation overnight at 30°C with permanent shaking in the dark. After washing three times in 1ml 50% DMF/0.1M Na_2CO_3 the beads were incubated in 1ml 1M ethanolamine for 6h at 30°C with permanent shaking in the dark followed by the denoted washing steps: 50% DMF/0.1M Na_2CO_3, then H_2O, then 0.1M $NaHCO_3$ pH 8.0/0.5M NaCl followed by 0.1M NaAc pH 4.0/0.1M NaCl and finally three times in chromatography buffer (see below) containing 150mM NaCl. As control matrix epoxy-activated Sepharose 6B was incubated with 1M ethanolamine and equally treated as described above. The beads were stored in 20% ethanol at 4°C in the dark.

Carbodiimide coupling: ECH-Sepharose 4B (Amersham Biosciences) was washed according to the manufacturer's instructions and equilibrated to 50% DMF / 50% ethanol. 2.5ml drained beads were resuspended in 5ml 15mM Compound 102 or Compound 103, respectively, dissolved in 50% DMF / 50% ethanol followed by drop by drop addition of 750μl 1M 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), dissolved in 50% DMF / 50% ethanol. The suspension was incubated overnight at room temperature with permanent end-over-end rotation and washed three times with 15ml 50% DMF / 50% ethanol prior to the addition of

5ml 33% DMF / 33% ethanol / 34% 1M ethanolamine pH 8.0 and 650µl EDC. After 2h incubation at room temperature with permanent end-over-end rotation, beads were washed three times with 15ml 50% DMF / 50% ethanol, twice with 15ml 0.5M NaCl and once with 15ml 20% ethanol. Control beads were incubated with 5ml 1M ethanolamine instead of compound and treated equally as described above. The beads were stored in 20% ethanol at 4°C in the dark.

Affinity chromatography and preparative gel electrophoresis.

1.25×10^9 PM1 cells were lysed in 15ml buffer containing 50mM HEPES pH 7.5, 400mM NaCl, 0.5% Triton X-100, 1mM EDTA, 1mM EGTA, 3mM $MgCl_2$, 1mM DTT plus additives (10mM sodium fluoride, 1mM orthovanadate, 10µg/ml aprotinin, 10µg/ml leupeptin, 1mM PMSF), cleared by centrifugation and adjusted to 1M NaCl. The filtered lysate was loaded with a flow rate of 100µl/min on a 25mM x 5mM chromatography column containing 500µl Compound 102 or Compound 103 matrix, respectively, equilibrated to chromatography buffer (20mM HEPES pH 7.5, 0.25 % Triton X-100, 1mM EDTA, 1mM EGTA) containing 1M NaCl. The column was washed with 25 column volumes, equilibrated to chromatography buffer containing 150mM NaCl and bound proteins were eluted in the same buffer containing 200µM Compound 102 or 200 µM Compound 103, respectively, 10mM ATP and 20mM $MgCl_2$ with a flow rate of 50µl/min. The volume of protein containing fractions was reduced to 1/5 in a SpeedVac concentrator prior to precipitation according to Wessel & Flügge (Wessel et al., 1984). Precipitated proteins were dissolved in 16-BAC sample buffer and after reduction/alkylation separated by 2-dimensional 16-BAC/SDS-PAGE (Daub et al., Journal of Virology 2002, 76, 8214-8137). Coomassie stained spots were picked and subjected to analysis by mass spectrometry.

Results:

Expression and kinase activity of CDK9/CyclinT1:

CDK9/CyclinT1 complexes from HEK293 cells were completely solubilised. CDK9/CyclinT1 proteins were almost completely precipitated by and eluted from streptavidin beads (data not shown). An imagination of the enrichment can be drawn from the blots stained for protein by PonceauS. CDK9/CyclinT1 proteins can be seen in the eluate whereas they are not visible within the cells or extract. Probing nitrocellulose with antibodies against CDK2 and CDK4 revealed that those kinases do not contaminate the purifications (data not shown).

As shown in figure 2 increasing amounts of CDK9 wt proteins incubated with substrates (ATP and GST-CTDII) resulted in incorporation of radioactive

phosphate. As exspected, mutation of critical kinase domain residues (K48R and D167N) within CDK9 revealed no phosphate incorporation, meaning that these mutations render the kinase inactive. Additionally, EDTA pre-incubation completely inhibited activity.

These results show that purification of CDK9/CyclinT1 proteins using adenovirus leads to an active and pure enzyme. A putative contamination with other protein kinases can be ruled out because purification of mutated CDK9 resulted in negligible kinase activity.

Table 2 shows the half-maximal inhibition constant (IC_{50}) values of the compounds according to the present invention on CDK9 and on CDK2, respectively.

Table 2: Inhibitory effect on CDK9 and CDK2 of compounds according to the present invention

Activity range "a" means, that the compounds do have an IC_{50} between 1 – 1000 nM, activity range "b" means, that the compounds do have an IC_{50} between 1000 – 10000 nM and activity range "c" means that the compounds do have an IC_{50} between 10000 and 250000 nM. All LCMS values relate to $(M + H)^+$ if not explicitly indicated as $(M - H)^-$

①: Compound Number ②: Method of synthesis according to scheme 1 – 12 ③: Retention time (minutes)

④: LC Method ⑤: CDK9 (activity range) ⑥: CDK4 (activity range) ⑦: CDK2 (activity range)

①	②	LCMS	③	④	Nomenclature	⑤	⑥	⑦
(1)	1	447	1.3	A1	N-{4-[6-(4-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-4-methylbenzene-sulfonamide	c		b
(2)	1	447	1.45	A1	N-{4-[6-(3-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-4-methyl-benzenesulfonamide	c		c
(3)	1	385	0.94	A1	N-{5-[6-(4-Methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane sulfonamide	b		a
(4)	1	488	1.16	A1	4-Amino-N-{4-[6-(2-benzyloxy-phenyl)-pyrimidin-4-yl-amino]-phenyl}-benzamide	a		b
(5)	1	447	1.16	A1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-4-methyl-benzene sulfonamide	a		a
(6)	1	412	0.8	A1	4-Amino-N-{4-[6-(4-methoxy-phenyl)-pyrimidin-4-yl-amino]-phenyl}-benzamide	a		b
(7)	1	383	1.95	B1	[6-(2-Benzyloxy-phenyl)-pyrimidin-4-yl]-(2-pyridin-4-yl-ethyl)-amine	a		b
(8)	1	412	0.76	A1	4-Amino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-yl-amino]-phenyl}-benzamide	a		b
(9)	1	361	0.78	A1	1-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-pyrrolidin-2-one	a	a	a
(10)	1	335	0.44	A1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-acetamide	a	b	a
(11)	1	433	1.07	A1	N-{4-[6-(4-Hydroxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-4-methyl-benzenesulfonamide	a		a
(12)	1	370	1.57	B1	N-{5-[6-(3-Amino-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane sulfonamide	a		a
(13)	1	292	1.27	B1	[6-(3-Amino-phenyl)-pyrimidin-4-yl]-(2-pyridin-4-yl-ethyl)-amine	b		b
(14)	1	321	1.52	B1	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benz-amide	a	c	a
(15)	1	336	2.21	B1	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzoic acid methyl ester	a		a
(16)	1	398	1.51	B1	4-Amino-N-{4-[6-(4-hydroxy-phenyl)-pyrimidin-4-yl-amino]-phenyl}-benzamide	b		b

(17)	1	487 $(M-H)^-$	1.24	A1	3-(4-{6-[4-(Toluene-4-sulfonylamino)-phenylamino]-pyrimidin-4-yl}-phenyl)-propionic acid	c		c
(18)	1	489	1.6	A1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-4-methyl-N-propyl-benzenesulfonamide	b		c
(19)	1	377	1.02	A1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2,2-dimethyl-propionamide	a		b
(20)	1	412	1.05	A1	2-Amino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide	a		b
(21)	1	397	1.52	B1	4-Amino-N-{4-[6-(3-amino-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide	b		b
(22)	1	293	1.61	B1	N-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-benzene-1,4-diamine	a	b	a
(23)	1 + 2	476	2.38	B1	4-Isopropyl-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzenesulfon-amide	a		b
(96)	1	461	2.24	B1	N-(4-{[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-methyl-amino}-phenyl)-4-methyl-benzenesulfon-amide	b		b
(24)	1	373 $(M-H)^-$	2.02	B1	N-[4-(6-Chloro-pyrimidin-4-ylamino)-phenyl]-4-methyl-benzenesulfonamide	c		b
(25)	1	338 $(M-H)^-$	1.57	B1	4-Amino-N-[4-(6-chloro-pyrimidin-4-ylamino)-phenyl]-benzamide	c		c
(26)	1+4+8	307	1.79	B1	N-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-N-methyl-benzene-1,4-diamine	b		b
(27)	1+4+8	505	1.28	A1	[{4-[6-(4-Hydroxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester	b		a
(28)	1	519	2.36	A1	[{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester	b		b
(29)	1 + 2	504	2.33	B1	(S)-2-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl carbamoyl}-piperidine-1-carboxylic acid tert-butyl ester	a		b
(30)	1 + 6	404	1.55	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a	a	b
(31)	1	442	1.78	B1	4-Amino-N-{4-[6-(2,4-dimethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide	a		a
(32)	1	408	1.91	B1	4-Amino-N-{4-[6-((E)-styryl)-pyrimidin-4-ylamino]-phenyl}-benzamide	c		c
(33)	1 + 2	371	1.81	B1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-methanesulfonamide	a	b	a

(34)	1 + 2	509	2.4	B1	Biphenyl-4-sulfonic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-yl-amino]-phenyl}-amide	b		b
(35)	1	454	2.12	B1	4-Amino-N-{4-[6-(5-isopropyl-2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide	c		c
(36)	1 + 2	415	1.21	A1	Bicyclo[2.2.1]heptane-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a		c
(37)	1 + 2	453	1.38	A1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-3-methyl-2-phenyl-butyramide	b		c
(38)	1 + 9	418	1.09	A1	1-Cyclohexyl-3-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-urea	a		b
(39)	1	446	2.01	B1	4-Amino-N-{4-[6-(5-chloro-2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide	b		c
(40)	1	487	1.43	B1	(E)-3-(3-{6-[4-(Toluene-4-sulfonylamino)-phenylamino]pyrimidin-4-yl}phenyl)acrylic acid	c		c
(41)	1 + 2	403	2.13	B1	Cyclohexanecarboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]phenyl}amide	b		c
(42)	1 + 2	391	2.07	B1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-3,3-dimethyl-butyramide	b		b
(43)	7	417	1.87	B1	4-Amino-N-{4-[6-(cyclohexylmethyl-amino)-pyrimidin-4-ylamino]-phenyl}-benzamide	b		c
(44)	1 + 3	403	2.13	B1	N-Cyclohexyl-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide	a		b
(45)	1 + 2	453	2.48	B1	4-tert-Butyl-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide	b		c
(46)	1 + 2	378	1.68	B1	2-Dimethylamino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-acetamide	a	b	b
(47)	1 + 2	504	2.12	B1	(1-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl-carbamoyl}-cyclo-pentyl)-carbamic acid tert-butyl ester	a		c
(48)	1 + 2	518	2.18	B1	2-({4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl-carbamoyl}-methyl)-piperidine-1-carboxylic acid tert-butyl ester	b		b
(49)	1 + 2	495	1.83	B1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-4-(4-methyl-piperazin-1-yl)-benzamide	a		b
(50)	1 + 2	398	1.66	B1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-isonicotinamide	b		c
(51)	1	442	1.58	B1	4-Amino-N-{4-[6-(2,6-dimethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide	b		c
(52)	1 + 2	397	2	B1	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N-phenyl-benzamide	a		c
(53)	1 + 5	3.35	1.02	A1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-guanidine	b		b
(54)	1 + 3	377	2.02	B1	N-tert-Butyl-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide	b		b

(55)	1	426	1.81	B1	4-Amino-N-{4-[6-(2-ethoxy-phenyl)-pyrimidin-4-yl-amino]-phenyl}-benzamide	a		b
(56)	1	442	1.69	B1	4-Amino-N-{4-[6-(2,3-dimethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide	b		b
(57)	1	442	1.71	B1	4-Amino-N-{4-[6-(2,5-dimethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide	c		c
(58)	1	440	1.87	B1	4-Amino-N-{4-[6-(2-isopropoxy-phenyl)-pyrimidin-4-yl-amino]-phenyl}-benzamide	a		a
(59)	1	418	1.45	B1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2-piperidin-2-yl-acet-amide	a	a	b
(60)	7	365	1.01	B1	4-Amino-N-{4-[6-(2-hydroxy-ethylamino)-pyrimidin-4-ylamino]-phenyl}-benzamide	b		c
(97)	1 + 2	427	1.62	A1	4-Amino-N-{4-[2-amino-6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide	b		c
(61)	1 + 2	455	2.48	B1	Adamantane-1-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	b		c
(62)	1	395	2.58	B1	(4-Benzooxazol-2-yl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine	c		c
(63)	1	394	1.88	B1	[4-(1H-Benzoimidazol-2-yl)-phenyl]-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine	a		a
(64)	1 + 2	418 $(M-H)^-$	1.74	A1	3-Diethylamino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-propionamide	a	b	b
(65)	1 + 2	452	1.98	B1	(S)-1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a	c	b
(66)	1 + 6	418	1.97	B1	1-Amino-cyclohexanecarboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a	b	b
(67)	1	383	1.35	B1	4-Amino-N-[4-(6-pyridin-4-yl-pyrimidin-4-ylamino)-phenyl]-benzamide	c		c
(87)	1 + 2	418	1.59	B1	1-Methyl-piperidine-3-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a	b	b
(98)	1	448	2.43	B1	Quinoline-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a		c
(68)	1 + 6	404	1.82	B1	1-Amino-cyclopentanecarboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a	b	b
(69)	1	404	1.53	B1	(R)-Piperidine-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a	a	b
(70)	1 + 2	401	1.59	B1	1-Methyl-1H-imidazole-4-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a		b
(71)	1 + 2	411	1.99	B1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2-phenyl-acetamide	a		b

(72)	1 + 3	305	1.55	C1	N-[4-(6-Chloro-pyrimidin-4-ylamino)-phenyl]-2,2-dimethyl-propionamide			c
(73)	1	348	1.57	B1	2,2-Dimethyl-N-[4-(6-pyridin-3-yl-pyrimidin-4-ylamino)-phenyl]-propionamide			c
(74)	7	381 $(M-H)^-$	1.26	B1	2,2-Dimethyl-N-{4-[6-(1-methyl-piperidin-4-ylamino)-pyrimidin-4-ylamino]-phenyl}-propionamide	c		c
(75)	1	389 $(M-H)^-$	1.12	B1	3-{6-[4-(2,2-Dimethyl-propionylamino)-phenylamino]-pyrimidin-4-yl}-benzoic acid	c		
(76)	1	380 $(M-H)^-$	1.67	B1	4-Amino-N-[4-(6-phenyl-pyrimidin-4-ylamino)-phenyl]-benzamide	b		c
(77)	1	386 $(M-H)^-$	1.64	B1	4-Amino-N-[4-(6-thiophen-2-yl-pyrimidin-4-ylamino)-phenyl]-benzamide	b		c
(78)	7	369	1.47	B1	2,2-Dimethyl-N-{4-[6-(4-methyl-piperazin-1-yl)-pyrimidin-4-ylamino]-phenyl}-propionamide			c
(79)	7	329	1.12	B1	N-{4-[6-(2-Amino-ethylamino)-pyrimidin-4-ylamino]-phenyl}-2,2-dimethyl-propionamide	c		c
(80)	7	342 $(M-H)^-$	1.24	B1	N-{4-[6-(3-Hydroxy-propylamino)-pyrimidin-4-ylamino]-phenyl}-2,2-dimethyl-propionamide	c		c
(81)	1 + 6	426	1.74	B1	(S)-2-Amino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2-phenyl-acetamide	a	b	b
(82)	1 + 6	440	1.86	B1	(S)-N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2-methylamino-2-phenyl-acetamide	a	b	b
(83)	1 + 6	416 $(M-H)^-$	1.45	B1	(R,R)/(S,S)-*N*-(2-Amino-cyclohexyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide	a	b	b
(84)	1 + 2	454	2.42	B1	Benzothiazole-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	b		c
(85)	1	453	2.31	B1	N-{4-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2,2-dimethyl-propionamide	a		b
(86)	1 + 6	402 $(M-H)^-$	1.41	B1	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N-piperidin-3-yl-benzamide	a	a	a
(89)	1 + 2	418	1.44	B1	1-Methyl-piperidine-4-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a	b	b

(90)	1 + 6	374 $(M-H)^-$	1.34	B1	(S)-Azetidine-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a		b
(91)	1 + 6	388 $(M-H)^-$	1.56	B1	(R)-Pyrrolidine-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a	b	b
(92)	1	307	1.54	B1	[6-(4-Methoxy-phenyl)-pyrimidin-4-yl]-(2-pyridin-4-yl-ethyl)-amine	c		c
(93)	1	307	1.49	B1	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(2-pyridin-4-yl-ethyl)-amine	b		c
(94)	1	293	1.79	B1	2-[6-(2-Pyridin-4-yl-ethylamino)-pyrimidin-4-yl]-phenol	b		c
(95)	1	397	1.8	B1	4-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-benz-amide	a	b	a
(99)	1	335	1.72	B1	[6-(2-Isopropoxy-phenyl)-pyrimidin-4-yl]-(2-pyridin-4-yl-ethyl)-amine	a		b
(100)	1	385	1.83	B1	N-{5-[6-(3-Methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane-sulfonamide	b		b
(101)	1	454	2.08	B1	2-Dimethylamino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2-phenyl-acetamide	a		b
(102)	1	364	1.33	C1	3-Amino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-yl-amino]-phenyl}-propionamide	a	a	b
(103)	1 + 12	455	1.37	C1	4-Amino-N-(4-{6-[2-(3-amino-propoxy)-phenyl]-pyrimidin-4-ylamino}-phenyl)-benzamide	a	c	b
(104)	1	412	0.76	B1	N-{3-[6-(3-Methanesulfonylamino-4-methyl-phenylamino)-pyrimidin-4-yl]-phenyl}-acetamide	a	c	b
(105)	1	371	1.54	B1	N-{5-[6-(3-Hydroxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane-sulfonamide	a	c	a
(106)	1	355	1.7	B1	N-[2-Methyl-5-(6-phenyl-pyrimidin-4-ylamino)-phenyl]-methanesulfonamide	a	c	a
(107)	1	423	2.16	B1	N-{2-Methyl-5-[6-(3-trifluoromethyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-methanesulfonamide	c	c	c
(108)	1	448	1.45	B1	N-{5-[6-(3-Methanesulfonylamino-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methanesulfonamide	b		a
(109)	1	432	1.71	B1	N-{5-[6-(3-Amino-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-benzene-sulfonamide	a		b
(110)	1	357	1.26	B1	N-[5-([4,5']Bipyrimidinyl-6-ylamino)-2-methyl-phenyl]-methanesulfonamide	b		b
(111)	1 + 9	456	1.84	B1	1-Benzo[1,3]dioxol-5-yl-3-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-urea			c
(112)	1 + 9	440	1.93	B1	1-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-3-(4-methyl-benzyl)-urea	a		c
(113)	1 + 9	392	1.81	B1	1-tert-Butyl-3-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-urea	a		b

(114)	1	415	2.08	B1	2,2-Dimethyl-N-{4-[6-(2-trifluoro-methyl-phenyl)-pyrimidin-4-yl-amino]-phenyl}-propionamide	c		c
(115)	1	321	1.47	B1	3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide	a		a
(116)	1	398	1.61	B1	Propane-1-sulfonic acid {5-[6-(3-amino-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-amide	a		a
(117)	1	342	1.07	C1	4-[6-(3-Amino-phenyl)-pyrimidin-4-ylamino]-benzene-sulfonamide	b		a
(118)	1	392	1.66	B1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2-methyl-2-methylamino-propionamide	a	a	b
(119)	1 + 10	391	1.76	C1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-3-methyl-phenyl}-2,2-dimethyl-propionamide	c		c
(120)	1 + 11	462	1.68	C1	N-{5-[6-(3-Amino-phenyl)-pyrimidin-4-ylamino]-2-benzyl-oxy-phenyl}-methane-sulfonamide	b		b
(121)	1	356	1.21	C1	N-{3-[6-(3-Amino-phenyl)-pyrimidin-4-ylamino]-phenyl}-methanesulfonamide	a		b
(122)	1	377	1.82	C1	N-{3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2,2-dimethyl-propionamide	b		b
(123)	1	307	1.35	C1	N*1*-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-2-methyl-benzene-1,4-diamine	b		b
(124)	1	293	1.43	C1	N-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-benzene-1,3-diamine	a	b	a
(125)	1	482	1.03	B1	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N-(4-morpholin-4-yl-phenyl)-benzamide	a		b
(126)	1	373	2.08	B1	2,2-Dimethyl-N-{4-[6-(2-vinyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-propionamide	b		c
(127)	1	365	2.03	B1	N-{4-[6-(2-Fluoro-phenyl)-pyrimidin-4-ylamino]-phenyl}-2,2-dimethyl-propionamide	c		c
(128)	1	404	1.92	B1	(S)-Piperidine-2-carboxylic acid {3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a	b	a
(129)	1	465	1.26	B1	2-Oxo-2H-chromene-3-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	c		
(130)	1	441	1.89	C1	Benzo[1,3]dioxole-5-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a		b
(131)	1	375	2.13	C1	N-{4-[6-(2-Ethyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-2,2-dimethyl-propionamide	c		b
(132)	1	423	2.19	C1	N-[4-(6-Biphenyl-2-yl-pyrimidin-4-ylamino)-phenyl]-2,2-dimethyl-propionamide	c		
(133)	1	436	1.07	C1	1H-Indole-3-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a		b

(135)	1	419	1.7	B1	N-((1R,2R) / (1S,2S)-2-Hydroxy-cyclohexyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benz-amide	a		b
(136)	1	413	0.91	B1	N-(4-Hydroxy-phenyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benz-amide	a		b
(137)	1	439	1.54	A1	N-(4-Isopropyl-phenyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benz-amide	b		c
(138)	1	437	1.34	B1	1H-Benzoimidazole-5-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	b		c
(139)	1	463	1.53	A1	1-Hydroxy-naphthalene-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a		b
(140)	1	406	1.82	B1	(2S,3S)-2-Amino-3-methyl-pentanoic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a	b	b
(141)	1	437	2.02	B1	1H-Indazole-3-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	b		
(142)	1	483	2.89	B1	Quinoline-8-sulfonic acid {5-[6-(3-amino-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-amide	a		c
(143)	1	392	1.69	B1	(S)-2-Amino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-3-methyl-butyramide	a	b	b
(144)	1	436	1.43	A1	1-Methyl-1H-imidazole-4-sulfonic acid {5-[6-(3-amino-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-amide	a		a
(145)	1	463	2.3	B1	3-Hydroxy-naphthalene-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	b		
(146)	1	476	1.81	C1	2-Amino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-yl-amino]-phenyl}-2-naphthalen-2-yl-acetamide	a		b
(147)	3	391	1.63	B1	{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-morpholin-4-yl-methanone	b	b	

(148)	3	418	1.76	C1	N-((1S,2R) / (1R,2S)--2-Amino-cyclohexyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benz-amide	a		b
(149)	1	426	1.69	B1	4-Amino-N-{4-[6-(2-methoxy-phenyl)-5-methyl-pyrimidin-4-ylamino]-phenyl}-benzamide	c		
(150)	1	357	1.64	B1	3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzene-sulfonamide	a	c	a
(151)	1	398	1.95	B1	4-Amino-N-{4-[6-(2-hydroxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide	c		c
(152)	1	307	1.51	B1	N-[6-(2-Methoxy-phenyl)-5-methyl-pyrimidin-4-yl]-benzene-1,4-diamine	c		c
(153)	1	399	1.61	C1	Propane-2-sulfonic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-yl-amino]-phenyl}-amide	a		a
(154)	1	399	1.6	C1	Propane-1-sulfonic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-yl-amino]-phenyl}-amide	a		a
(155)	1	433	1.79	C1	N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzenesulfonamide	a		a
(156)	1	461	2.09	C1	N-{5-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane-sulfonamide	a		a
(157)	1	398	1.7	C1	N-{5-[6-(3-Dimethylamino-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane-sulfonamide	a		b
(158)	1	413	1.78	C1	N-{5-[6-(2-Isopropoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane-sulfonamide	a		a
(159)	1	519	2.31	B1	N-Bis-propane-1-sulfonic acid-{4-[6-(2-methoxy-phenyl)-5-methyl-pyrimidin-4-yl-amino]-phenyl}-amide	c		
(160)	1	413	1.85	B1	Propane-1-sulfonic acid {4-[6-(2-methoxy-phenyl)-5-methyl-pyrimidin-4-ylamino]-phenyl}-amide	c		
(161)	3	418	1.57	B1	N-(1R,2R)/(1S,2S) (2-Amino-cyclo-hexyl)-4-[6-(4-methoxy-phenyl)-pyrimidin-4-ylamino]-benz-amide	a		b
(162)	1	385	1.55	C1	N-{5-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane sulfonamide	a		a
(163)	1	380	1.58	C1	N-{5-[6-(3-Cyano-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane sulfonamide	b		b

(164)	1	480	1.95	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(2-benzyloxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a		a
(165)	1	383	1.49	C1	N-{5-[6-(3-Formyl-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane sulfonamide	b		b
(166)	1	385	1.34	C1	N-{5-[6-(2-Hydroxymethyl-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane sulfonamide	b		
(167)	1	404	1.61	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(4-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	b		
(168)	1	402	1.5	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(3-formyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	b	b	
(169)	1	417	1.72	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(3-dimethyl-amino-phenyl)-pyrimidin-4-yl-amino]-phenyl}-amide	b		
(170)	1	404	1.36	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(2-hydroxy-methyl-phenyl)-pyrimidin-4-yl-amino]-phenyl}-amide	b		
(171)	1	405	1.45	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(2-methoxy-pyridin-3-yl)-pyrimidin-4-yl-amino]-phenyl}-amide	a	b	b
(172)	1	405	1.45	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(6-methoxy-pyridin-3-yl)-pyrimidin-4-ylamino]-phenyl}-amide	b		
(173)	1	480	2.1	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(4-benzyloxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	c		
(174)	1	466	1.94	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(4-phenoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a		b
(175)	1	385	1.16	C1	N-{5-[6-(4-Hydroxymethyl-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane-sulfonamide	b		
(176)	1	386	1.43	C1	N-{5-[6-(2-Methoxy-pyridin-3-yl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane-sulfonamide	a		b

(177)	1	431	1.3	C1	(S)-Piperidine-2-carboxylic acid {4-[6-(4-acetylamino-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	b		
(178)	1	467	1.37	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(3-methanesulfonyl-amino-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a		
(179)	1	416	1.43	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(3-acetyl-phenyl) -pyrimidin-4-yl-amino]-phenyl}-amide	c		
(180)	1	485	1.62	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(4-cyclopentyl-carbamoyl-phenyl)-pyrimidin-4-yl-amino]-phenyl}-amide	b		
(181)	1	371	1.89	C1	N-{5-[6-(2-Hydroxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane-sulfonamide	a		a
(182)	1	439	1.85	C1	(E)-3-{3-[6-(3-Methanesulfonylamino-4-methyl-phenyl-amino)-pyrimidin-4-yl]-phenyl}-acrylic acid methyl ester	b		b
(183)	1	385	1.34	C1	N-{5-[6-(3-Hydroxymethyl-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane-sulfonamide	b		b
(184)	1	413	2.22	C1	N-Butyl-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide	a		b
(185)	1	356	1.81	C1	(3-Methanesulfonyl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine	a		a
(186)	1	433	1.59	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(2,3-dimethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	b	b	c
(187)	1	433	1.64	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(2,4-dimethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a	a	b
(188)	1	432	1.85	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(2-isopropoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a	a	b
(189)	1	420	1.63	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(2-methylsulfanyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	a	a	b

(190)	1	458	1.84	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(2-trifluoromethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	b	b	
(191)	1	422	1.55	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(5-acetyl-thio-phen-2-yl)-pyrimidin -4-ylamino]-phenyl}-amide	b		
(192)	1	408	1.65	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(2-chloro-phenyl) -pyrimidin-4-yl-amino]-phenyl}-amide	a		c
(193)	1	404	1.31	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(3-hydroxy-methyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	b		
(194)	3	404	1.34	B1	N-((1R,2R) / (1S,2S)-2-Amino-cyclo-hexyl)-4-[6-(3-hydroxy-phenyl)-pyrimidin-4-yl-amino]-benzamide	b		
(195)	3	481	1.36	B1	N-((1R,2R) / (1S,2S)-2-Amino-cyclohex-yl)-4-[6-(3-methane sulfonylamino-phenyl)-pyrimidin -4-ylamino]-benzamide	a		b
(196)	3	445	1.44	B1	4-[6-(2-Acetyl-amino-phenyl)-pyrimidin-4-yl-amino]-N-((1R,2R) / (1S,2S)-2-amino-cyclohexyl)-benz-amide	c		
(197)	1	399	1.71	B1	N-{5-[6-(2-Methoxymethyl-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane-sulfonamide	b		
(198)	3	494	1.91	B1	N-((1R,2R) / (1S,2S)-2-Amino-cyclohexyl)-4-[6-(2-benzyloxy-phenyl)-pyrimidin-4-yl-amino]-benzamide	a	a	a
(199)	3	446	1.81	B1	N-((1R,2R) / (1S,2S)-2-Amino-cyclohex-yl)-4-[6-(2-isopro-poxy-phenyl)-pyrimidin-4-ylamino]-benzamide	a	b	b
(200)	1	426	1.75	B1	4-Amino-N-{4-[6-(4-methoxy-phenyl)-5-methyl-pyrimidin-4-ylamino]-phenyl}-benzamide	c		
(201)	3	446	1.67	B1	3-{6-[4-((1R,2R) / (1S,2S)-2-Amino-cyclohexylcarbamoyl)-phenylamino]-pyrimidin-4-yl}-benzoic acid methyl ester	b		
(202)	1	406	1.26	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(4-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	c		

(203)	1	418	1.48	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(3-methoxymethyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	b		
(204)	1	307	1.59	B1	N-[6-(2-Methoxy-phenyl)-2-methyl-pyrimidin-4-yl]-benzene-1,4-diamine	c		
(205)	1	307	1.68	B1	N-[6-(4-Methoxy-phenyl)-2-methyl-pyrimidin-4-yl]-benzene-1,4-diamine	c		
(206)	3	403	1,27	B1	N-((1R,2R)/(1S,2S)-2-Amino-cyclohexyl)-4-[6-(3-amino-phenyl)-pyrimidin-4-ylamino]-benzamide	b		
(207)	3	445	1,3	B1	4-[6-(3-Acetylamino-phenyl)-pyrimidin-4-ylamino]-N-((1R,2R)/(1S,2S)-2-amino-cyclohexyl)-benzamide	b		
(208)	3	494	2,09	B1	N-((1R,2R)/(1S,2S)-2-Amino-cyclohexyl)-4-[6-(4-benzyloxy-phenyl)-pyrimidin-4-ylamino]-benzamide	c		
(209)	3	413	1,59	B1	N-((1R,2R)/(1S,2S)-2-Amino-cyclohexyl)-4-[6-(3-cyano-phenyl)-pyrimidin-4-ylamino]-benzamide	b		
(210)	3	432	1,49	B1	N-((1R,2R)/(1S,2S)-2-Amino-cyclohexyl)-4-[6-(2-methoxymethyl-phenyl)-pyrimidin-4-ylamino]-benzamide	b		
(211)	3	431	1,58	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(3-dimethylaminomethyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide	b		
(212)	3	439	1,53	B1	N-((1R,2R)/(1S,2S)-2-Amino-cyclohexyl)-4-(6-quinolin-3-yl-pyrimidin-4-ylamino)-benzamide	c		
(213)	3	420	1,28	B1	N-((1R,2R)/(1S,2S)-2-Amino-cyclohexyl)-4-(2'-methoxy-[4,5']bipyrimidinyl-6-ylamino)-benzamide	c		
(214)	1	342	1,31	B1	3-[6-(3-Amino-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide	a		b
(215)	1	357	1,45	B1	3-[6-(4-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide	a		a
(216)	1	418	2,43	B2	(R,R)-N-(2-Amino-cyclohexyl)-4-[6-(2-hydroxymethyl-phenyl)-pyrimidin-4-ylamino]-benzamide			
(217)	1	420	3,05	B2	N-(2-Diethylamino-ethyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide		b	
(218)	1	404	3,1	B2	(R,R)-N-(2-Amino-cyclohexyl)-4-[6-(2-hydroxy-phenyl)-pyrimidin-4-ylamino]-benzamide		b	
(219)	1	419	1,46	B1	(R,R)-N-(2-Amino-cyclohexyl)-4-[6-(2-methoxy-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide		c	

(220)	1	445	1,76	B1	(R,R)-N-(2-Amino-cyclohexyl)-4-[6-(5-dimethylaminomethyl-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide			
(221)	1	459	1,28	B1	(R,R)-5-{6-[4-(2-Amino-cyclohexylcarbamoyl)-phenylamino]-pyrimidin-4-yl}-pyridine-2-carboxylic acid dimethylamide			
(222)	1	434	1,78	B1	(R,R)-N-(2-Amino-cyclohexyl)-4-[6-(6-methylsulfanyl-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide			
(223)	1	417	1,41	B1	(R,R)-N-(2-Amino-cyclohexyl)-4-[6-(5-aminomethyl-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide			
(224)	1	434	1,59	B1	(R,R)-N-(2-Amino-cyclohexyl)-4-[6-(4-methylsulfanyl-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide		b	
(225)	1	418	1,26	B1	N-(2-Amino-cyclohexyl)-4-[6-(5-hydroxymethyl-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide			
(226)	3	390	5,33	D2	rac-4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N-pyrrolidin-3-yl-benzamide			
(227)	1	431	2,85	B2	(R,R)-N-(2-Amino-cyclohexyl)-4-[6-(5-dimethyamino-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide			
(228)	1	436	1,52	B1	(R,R)-4-[6-(5-Acetyl-thiophen-2-yl)-pyrimidin-4-ylamino]-N-(2-amino-cyclohexyl)-benzamide			
(229)	1	496	3,66	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[3-(piperidine-1-sulfonyl)-phenyl]-amine N-(2-diethylamino-ethyl)-benzamide		a	
(230)	1	430	1,43	B1	(R,R)-4-[6-(2-Acetyl-phenyl)-pyrimidin-4-ylamino]-N-(2-amino-cyclohexyl)-benzamide			
(231)	3	398	6,63	D2	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N-pyridin-3-yl-benzamide			
(232)	1	446	2,73	B2	N-(1-Acetyl-piperidin-3-yl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide			
(233)	1	431	2,89	B2	(R,R)-N-(2-Amino-cyclohexyl)-4-[6-(2-dimethylamino-phenyl)-pyrimidin-4-ylamino]-benzamide		b	
(234)	8A	548	7,55	D2	4-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzoylamino}-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester			
(235)	1	391	3,06	B2	2-Chloro-5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			
(236)	1	425	3,75	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[3-(piperidine-1-sulfonyl)-phenyl]-amine			
(237)	1	397	3,29	B2	N-Allyl-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			
(238)	1	447	3,56	B2	N-Benzyl-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			

(239)	1	411	3,8	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[3-(pyrrolidine-1-sulfonyl)-phenyl]-amine			
(240)	1	427	3,31	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[3-(morpholine-4-sulfonyl)-phenyl]-amine			
(241)	1	371	3,08	B2	3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide			
(242)	1	399	2,83	B2	N-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-N-(3-sulfamoyl-phenyl)-acetamide			
(243)	1	437	3,84	B2	N,N-Diallyl-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			
(244)	1	433	3,24	B2	3-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			
(245)	1	465	3,69	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[4-(4-nitro-benzenesulfonyl)-phenyl]-amine			
(246)	1	410	3,98	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-trifluoromethanesulfonyl-phenyl)-amine			
(247)	1	356	3,07	B2	(4-Methanesulfonyl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(248)	1	452	2,34	B2	N-(3,4-Dimethyl-isoxazol-5-yl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			
(249)	1	399	3,37	B2	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N-propyl-benzenesulfonamide			
(250)	1	357	2,84	B2	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			
(251)	1	385	3,38	B2	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N,N-dimethyl-benzenesulfonamide			
(252)	1	415	3,09	B2	N-(2-Methoxy-ethyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			
(253)	1	432	3,49	B2	[6-(2-Benzyloxy-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine			
(254)	1	342	3,31	B2	2-[6-(3-Methanesulfonyl-phenylamino)-pyrimidin-4-yl]-phenol			
(255)	1	341	2,62	B2	[6-(3-Amino-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine			
(256)	1	372	2,42	B2	5-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-benzenesulfonic acid			
(257)	1	386	2,77	B2	2-{3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonyl}-ethanol			
(258)	1	374	3,1	B2	(2-Fluoro-5-methanesulfonyl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(259)	1	341	2,97	B2	[6-(2-Amino-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine			
(260)	1	410	3,92	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(3-trifluoromethanesulfonyl-phenyl)-amine			
(261)	1	418	3,54	B2	(3-Methanesulfonyl-phenyl)-[6-(2-Phenoxy-phenyl)-pyrimidin-4-yl]-amine			
(262)	1	398	3,55	B2	[6-(2-Butoxy-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine			

(263)	1	368	3,29	B2	(3-Ethenesulfonyl-phenyl-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(264)	1	420	1,81	B1	(S)-Piperidine-2-carboxylic acid {4-[6-(4-methylsulfanyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide			
(265)	1	370 & 372	4,28	D1	2-Chloro-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzoic acid methyl ester			
(266)	1	384	3,82	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-phenoxy-benzyl)-amine			
(267)	1	350	3,98	D1	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-3-methyl-benzoic acid methyl ester			
(268)	1 + 2	382	5,87	D2	[6-(3-Amino-phenyl)-pyrimidin-4-yl]-(1-methanesulfonyl-2,3-dihydro-1*H*-indol-6-yl)-amine			
(269)	1	385	3,36	B2	3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester			
(270)	1	336	2,11	B2	{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-acetic acid			
(271)	1	318	2,87	B2	(1*H*-Indazol-6-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(272)	1	348	3,81	B2	1-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-butan-1-one			
(273)	1	285	2,49	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-piperidin-3-yl-amine			
(274)	1	382	3,98	B2	{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-phenyl-methanone			
(275)	1	369	3,9	B2	*N*-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-*N'*-phenyl-benzene-1,3-diamine			
(276)	1	364	3,31	B2	(3-[1,3]Dioxan-2-yl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(277)	1	308	3,46	B2	(3-Methoxy-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(278)	1	308	3,29	B2	(4-Methoxy-phenyl)-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-amine			
(279)	1	369	3,81	C2	*N*-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-*N'*-phenyl-benzene-1,4-diamine			
(280)	1	363	3,16	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-morpholin-4-yl-phenyl)-amine		**b**	
(281)	1	296	3,43	B2	(2-Fluoro-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(282)	1	375	3,41	B2	(1-Benzyl-piperidin-4-yl)-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-amine			
(283)	1	334	4,29	B2	(4-Butyl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(284)	1	370	3,98	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-phenoxy-phenyl)-amine			
(285)	1	371	2,66	B2	4-{[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide			
(286)	1	395	3,17	B2	rac-1-Dimethylamino-3-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenoxy}-3-propan-2-ol			

(287)	1	307	2,72	B1	*N*-[6-(4-Methoxy-phenyl)-5-methyl-pyrimidin-4-yl]-benzene-1,4-amine			
(288)	1	292	2,45	B1	*N*-[6-(3-Amino-phenyl)-5-methyl-pyrimidin-4-yl]-benzene-1,4-amine			
(289)	1	285	2,5	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-piperidin-4-yl-amine			
(290)	1	461	3,98	B2	4-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester			
(291)	1	284	3,5	B2	Cyclohexyl-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(292)	9A	433 $(M-H)^-$	7,05	D2	4-{6-[2-(2-Morpholin-4-yl-ethoxy)-phenyl]-pyrimidin-4-ylamino}-benzoic acid methyl ester			
(293)	1	366	3,75	D1	2-Methoxy-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzoic acid methyl ester			
(294)	1	412	2,42	B2	{4-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-acetic acid		b	
(295)	1	323	3,6	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(3-nitro-phenyl)-amine			
(296)	1	308	2,79	B2	{3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-methanol			
(297)	1	354	3,87	B2	[6-(2-Benzyloxy-phenyl)-pyrimidin-4-yl]-phenyl-amine			
(298)	1	278	3,43	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-phenyl-amine			
(299)	1	296	3,45	B2	(4-Fluorophenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(300)	1	370	4,07	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(3-phenoxy-phenyl)-amine			
(301)	1	324	3,71	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(3-methylsulfanyl-phenyl)-amine			
(302)	1	361	3,32	B2	[6-(2-Benzyloxy-phenyl)-pyrimidin-4-yl]-piperidin-4-yl-amine			
(303)	1	294	2,89	B2	3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenol			
(304)	1	320	3,31	B2	1-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-ethanone			
(305)	1	356 & 358	2,42	D1	2-Chloro-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzoic acid			
(306)	1	371 $(M-H)^-$	4,93	D1	{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-butyl}-carbamic acid tert-butyl ester			
(307)	1 + 2	473	8,87	D3	[6-(2-Benzyloxy-phenyl)-pyrimidin-4-yl]-(1-methanesulfonyl-2,3-dihydro-1*H*-indol-6-yl)-amine			
(308)	1	385	3,41	B2	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester			
(309)	1	321	7,42	D2	4-[6-(2-Amino-phenyl)-pyrimidin-4-ylamino]-benzoic acid methyl ester			

(310)	1	324	3,8	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-methylsulfanyl-phenyl)-amine			
(311)	1	273	2,2	D1	*N*^{1}-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-butane-1,4-diamine			
(312)	1	471	3,74	B2	1-{4-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-phenoxy}-3-dimethylamino-propan-2-ol			
(313)	1 + 2	397	3,6	D1	(1-Methanesulfonyl-2,3-dihydro-1*H*-indol-6-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(314)	1	445	2,69	B2	*N*-(2-Amino-cyclohexyl)-4-[6-(benzotriazol-1-yloxy)-pyrimidin-4-ylamino]-benzamide			
(315)	1	545	2,02	B2	(2-{4-[6-(Benzotriazol-1-yloxy)-pyrimidin-4-ylamino]-benzoylamino}-cyclohexyl)-carbamic acid tert-butyl ester			
(316)	1	320	3,41	C2	1-{3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-ethanone			
(317)	1	361	3,96	C2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-piperidin-1-yl-phenyl)-amine			
(318)	1	352	3,72	D1	3-Hydroxy-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzoic acid methyl ester			
(319)	1	352	4,25	D1	2-Hydroxy-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzoic acid methyl ester			
(320)	10A	442	5,87	D4	4-Amino-butane-1-sulfonic acid {5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-amide			
(321)	1				(3-{6-[3-(4-Amino-butane-1-sulfonylamino)-4-methyl-phenylamino]-pyrimidin-4-yl}-phenyl)-carbamic acid *9H*-fluoren-9-ylmethyl ester			
(322)	1	366	4,22	D1	3-Methoxy-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzoic acid methyl ester			
(323)	9A	434	5,67	D3	4-{6-[2-(2-Piperidin-1-yl-ethoxy)-phenyl]-pyrimidin-4-ylamino}-benzoic acid methyl ester			
(324)	9A	393	5,37	D3	4-{-6-[2-(2-Dimethylamino-ethoxy)-phenyl]-pyrimidin-4-ylamino}-benzoic acid methyl ester			
(325)	9A	449	5,2	D3	4-{-6-[2-(2-Diisopropylamino-ethoxy)-phenyl]-pyrimidin-4-ylamino}-benzoic acid methyl ester			
(326)	9A	422	5,67	D3	4-{-6-[2-(2-Diethylamino-ethoxy)-phenyl]-pyrimidin-4-ylamino}-benzoic acid methyl ester			
(327)	8A	448	4,03	D2	(S,S)-4-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzoylamino}-pyrrolidine-2-carboxylic acid methyl ester			
(328)	8A	434	4,52	D5	(S,S)-4-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzoylamino}-pyrrolidine-2-carboxylic acid			
(329)	8A	547	5,95	D3	(S,S)-6-[(4-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzoylamino}-pyrrolidine-2-carbonyl)-amino]-hexanoic acid			

(330)	3	389	7,32	D2	*N*-Cyclopentyl-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide			
(331)	1	357	2.82	B2	3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide		c	
(332)	1	356	3.70	B2	(3-Methanesulfonyl-phenyl)-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-amine			
(333)	1	386	2.77	B2	2-{3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfoyl}-ethanol			
(334)	1	463	2.70	B2	*N*-(4,6-Dimethyl-pyrimidin-2-yl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			
(335)	1	440	2.54	B2	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-*N*-thiazol-2-yl-benzenesulfonamide			
(336)	1	375	3.63	B2	(1-Benzyl-piperidin-3-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(337)	1	313	2.62	B2	3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-azepan-2-one			
(338)	1	433	3.49	B2	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-*N*-phenyl-benzenesulfonamide			
(339)	1	332	3.77	B2	rac-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(1,2,3,4-tetrahydro-naphthalen-1-yl)-amine			
(340)	1	341	2.89	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine			
(341)	1	371	3.07	B2	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-*N*-methyl-benzenesulfonamide		b	
(342)	1	366	3.24	B2	(1,1-Dioxo-1*H*-1λ^6–benzo[*b*]thiophen-6-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine		c	
(343)	1	399	2.12	B2	*N*-Acetyl-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			
(344)	1	463	3.32	B2	*N*-(2,6-Dimethyl-pyrimidin-4-yl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			
(345)	1	425	3.73	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[4-(piperidine-1-sulfonyl)-phenyl]-amine			
(346)	1	477	3.89	B2	3-{3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenoxy}-piperidine-1-carboxylic acid tert-butyl ester			
(346)	1	374	2.86	B2	[6-(2-Fluoro-6-methoxy-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine		b	
(348)	1	374	3.18	B2	[6-(4-Fluoro-2-methoxy-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine			
(349)	1	374	3.20	B2	[6-(5-Fluoro-2-methoxy-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine			
(350)	1	279	2.80	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-pyridin-3-yl-amine			
(351)	1	322	2.81	B2	2-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-ethanol		b	
(352)	1	431	2.38	B2	(9,9-Dioxo-9,10-dihydro-9λ^6–thia-10-aza-phenanthren-3-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(353)	1	332	2.99	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(1-methyl-1*H*-indazol-6-yl)-amine		b	

(354)	1	336	3.81	B2	Benzo[1,2,5]thiadiazol-4-yl-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(355)	1	336	3.62	B2	Benzo[1,2,5]thiadiazol-5-yl-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(356)	1	377	3.53	B2	rac-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[3-(piperidin-3-yloxy)-phenyl]-amine			
(357)	1	502	4.24	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-{1-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-1*H*-indazol-5-yl}-amine			
(358)	1	317	3.06	B2	(1*H*-Indol-5-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(359)	1	340	2.74	B2	(3-Methanesulfinyl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(360)	1	318	2.74	B2	(1*H*-Indazol-5-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(361)	1	342	401	B2	4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-thiophene-3-carboxylic acid methyl ester			
(362)	1	370	2.80	B2	4-Methanesulfonyl-benzyl-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(363)	1	352	3.37	B2	(5-Chloro-1*H*-indazol-3-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			
(364)	1	283	3.19	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(5-methyl-isoxazol-3-yl)-amine			
(365)	1	385	3.45	B2	3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-*N,N*-dimethyl-benzenesulfonamide			
(366)	1	385	3.27	B2	*N*-Ethyl-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			
(367)	1	399	3.46	B2	3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-*N*-propyl-benzenesulfonamide			
(368)	1	331	3.24	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(2-methyl-1*H*-indol-5-yl)-amine			
(369)	1	413 $(M-H)^-$	3.12	B2	*N*-(2-Methoxy-ethyl)-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			
(370)	1	413	3.5	B2	*N*-tert-Butyl-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide			
(371)	1	293	2.71	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-pyridin-2-ylmethyl-amine			
(372)	1	293	2.61	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-pyridin-3-ylmethyl-amine			
(373)	1	293	2.59	B2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-pyridin-4-ylmethyl-amine			
(374)	1	371	3.15	B2	5-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-benzenesulfonamide			
(375)	1	429	3.45	B2	*N*-(2-Methoxy-ethyl)-5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-benzenesulfonamide			
(376)	1	415	3.03	B2	*N*-(2-Hydroxy-ethyl)-5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-benzenesulfonamide			
(377)	1	348	2.17	A2	N,N-Diethyl-N'-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-benzene-1,4-diamine			

(378)	1	528	3,78	A2	1-(4-Chloro-3-trifluoromethyl-phenyl)-3-{5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-urea			
(379)	1	431	3,27	A2	1-Cyclohexyl-3-{5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-urea			
(380)	1	346	3,14	A2	[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-pyrrolidin-1-yl-phenyl)-amine			
(381)	1	326	2.74	A2	4-Chloro-N-1-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-benzene-1,3-diamine			
(382)	1	391	3,35	A2	1-Isopropyl-3-{5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-urea			
(383)	1	462	2.80	A2	1-{5-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-3-(2-morpholin-4-yl-ethyl)-urea			
(384)	1		2.79	A2	1-(2-Dimethylamino-ethyl)-3-{5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-urea			
(385)	1	356	3,81	A2	(4-Chloro-3-nitro-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine			

RNA-polymerase II phosphorylation:

In order to see, if the compounds according to the general formula (I) do have the intrinsic capacity to penetrate cells and act against cellular target proteins, especially CDK9, the effect of Compound 30 on CDK9-dependent phosphorylation of RNA-polymerase II was investigated. Probing blots with antibodies against the phosphorylated forms of RNA polymerase II showed, that specifically serine 2 phosphorylation was decreased, whereas antibodies recognizing serine 5 phosphorylation did not show any differences. These results indicate, that kinases being responsible for the phosphorylation of this site, for example CDK7 are not touched. Additionally, a reduction in the molecular weight of RNA polymerase II was observed indicating that phosphorylation is decreased (data not shown).

Growth of PM1 cells:

The growth of PM1 cells is not generally affected by compounds according to the present invention as shown by the results, summarized in Table 3. Indeed, only a small proportion of the compounds seem to affect severely the growth of PM1 cells. Those compounds, Compound 9 and Compound 28, had a tendency to inhibit potently CDK2. Therefore the observed effect on growth might be a cell cycle arrest more than toxicity towards the cells.
Additionally, no correlation between CDK9 inhibition and toxicity is observed.

Table 3: Growth inhibition by described compounds (the numbers are growth rates compared to rates of DMSO treated cells given in %).

Compound No	Growth after 7 days [% at 1 μM]
Compound 9, 28	≤ 50
Compound 1, 2, 3, 4, 5, 6, 8, 10, 11, 15, 18, 19, 20, 22, 25, 30	51 – 100
Compound 7, 17, 21, 29	101 – 150

HIV replication in PM1 cells:

Compounds according to the general formula (I) are potent inhibitors of HIV replication. Table 4 shows the inhibition of HIV replication (% of DMSO control [= 0%]) in cell culture of Compound 4, Compound 12, Compound 13, Compound 14, Compound 16, Compound 27, Compound 31, Compound 32, Compound 38, Compound 58, Compound 59, Compound 82, Compound 83, Compound 86, Compound 91, Compound 95, Compound 109, Compound 112, and Compound 116.

As is evident from Table 4 representative examples for the most effective compounds of those tested in inhibiting the HIV replication are compound 4, compound 12, compound 14, compound 27, compopund 58, compound 82, compound 83, compound 86, compound 95, compound 112 and compound 116 reducing HIV replication by over 60%. With compound 13, compound 16, compound 31, compound 32, compound 38, compound 59, compound 91 and compound 109 satisfactory results regarding inhibition of HIV replication were obtained (between 20 and 60% inhibition).

Table 4: Relative inhibition of HIV replication

Compound	[%] Inhibition of HIV Replication
Compound 13, 16, 31, 32, 38, 59, 91, 109	20 – 60
Compound 4, 12, 14, 27, 58, 82, 83, 86, 95, 112, 116	61 – 95

Selectivity panel data:

Table 5 shows the inhibitory effect of selected compounds according to the present invention on the activity of certain protein kinases. The activity of these protein kinases is depicted as % inhibition in the presence of 10 μM of compound in comparison to DMSO (0 % inhibition).

Table 5: Selectivity panel data (% inhibition) of selected compounds according to the present invention (Cpd. = Compound, n.a. = not available; inhibition greater than 80%: a; inhibition between 80 and 50%: b; inhibition between 50 and 30%: c;).

Cpd. No.	Abl	CDK1	CDK5	EGFR	GSK-3ß	PDGFR	c-Kit	p56 Lck	c-Src	RSK1	cMet
4		a		c	a			a			
6		a			b	c	b	c			
8		a					b	b			
9		a		b	b	c	c	b		c	
10		a		b	b	c	b	b			
12		a		a	a	c	b	b			
22		a		a	c	c	b	b			
30	b	a		a	c	c	b	b	b		c
33		a		b	b	b	b	b		c	
38		b		c	c	b	b	b			

49	b	a		b	b	c	b	b			
58		a		b	a			a			
59	b	a		a		b	b	b			
64	b	a		a	c	b	b	b			
65	b	b		a		b	b	b			
66	b	b		a		b	b	b			
68	b	b		a		b	b	b			
69	b	b		a		b	b	a			
70	c	a		b	b	b	b	b		b	
71		a		c	c	b	b	b			
81	b	a	a	b	b	b					
82	c	b	b	a	c	c					
83	c	a		b	c	b	b	b	b		b
86	c	a		a	b	b		b			
87	b	a		a		b	b	b		b	c
91	b	b		a	c	b		b			
95		a		b	a	c		b	b		
102	c	b	a	a		b					
103		b	b	a	b	c					
109		a	a	b	a	c					
116		a		a	a	c		b			
118	c	b	b	a		b					

These data show, that compounds according to the present invention, do have an inhibitory effect on the protein kinase activity of various protein kinases, such as Abl, CDK1, CDK5, EGFR. GSK-3ß, PDGFR, c-kit and p56Lck. Additionally c-Src, RSK1 and cMet were affected by some cpds in their activity (Table 5).

Impact on NFκB-dependent transcriptional acitivtiy:

It is known, that CDK9 regulates the NFκB-dependent transciptional acitivtiy. With Compound 4, Compound 7 and Compound 30 studies were done, to evaluate their effect on NFκB-dependent transciptional acitivtiy. Compound 30 was able, to affect TNF-α stimulated NFκB-dependent promotor activity at 1μM final concentration as shown in figure 3. Interestingly under non-stimulated conditions no inhibition was observed. Compound 4 and Compound 7 inhibited NFκB less effectively, closely reflecting the IC_{50} values of these compounds on CDK9/Cyclin T1. A titration of these three compounds showed EC_{50} values of about 2 μM for Compound 4 and 1 μM for Compound 30.

HBV replication

Selected compounds according to the present invention were tested in a HBV replication assay. As the results, depicted in figure 4 show, only Compound 7 inhibited replication without affecting viability in those cells. Compound 30 was inactive in those assays indicating that other protein kinase targets than CDK9 (especially further CDKs) might be important for HBV replication. This is underlined by flavopiridol, which inhibits replication, but is known to be a more or less unspecific inhibitor of CDKs.

HCMV replication:

Compounds according to the present invention were identified as potent inhibitors of HCMV replication in cell culture (see Figure 5):

Compound 4, Compound 6 and Compound 30 showed inhibition of HCMV replication (using strain AD 169 in HFF cells).

Affinity chromatography and preparative gel electrophoresis:

Compound 102 or Compound 103, known as Cyclin-dependent kinase 9 (CDK9) inhibitors were covalently coupled to ECH-Sepharose and used as media for affinity chromatography as described above.

Results from analysis by mass spectrometry revealed that both affinity media were able to isolate CDK9 out of crude PM1 cell lysates. Furthermore, both affinity media described here were able to identify additional targets for these compound molecules known to inhibit Cyclin-dependent kinase 9 (CDK9). In particular Ca^{2+}/Calmodulin-dependent protein kinase II γ (CaMK2γ), Ca^{2+}/Calmodulin-dependent protein kinase II δ (CaMK2δ), Cyclin-dependent kinase 2 (CDK2) and mixed lineage kinase-related kinase (MRK-beta, ZAK) were specifically bound by compound 102. In contrast, Glycogen synthase kinase 3 beta (GSK3β) and c-Src tyrosine kinase (CSK) were specifically bound by compound 103.

LCMS analysis of eluates reproduced those results. Furthermore, within this last set of experiments the following protein kinases were identified: For Compound 102 Ca^{2+}/Calmodulin-dependent protein kinase II β (CaMK2β), mixed lineage kinase (MLK, MRK-alpha), the src-like kinase yes, human cdc2-like protein kinase (similar to CDC2L5), CrkRS (Crk7, CDC2-related protein kinase 7), and Male germ cell-associated kinase (MAK) were identified.

For Compound 103 Ca^{2+}/Calmodulin-dependent protein kinase II β (CaMK2β), Glycogen synthase kinase 3 α (GSK3α), Cyclin-dependent kinase 2 (CDK2), CrkRS (Crk7, CDC2-related protein kinase 7), and a growth factor receptor similar to fibroblast growth factor receptor 3 (FGFR-3) sequences were detected.

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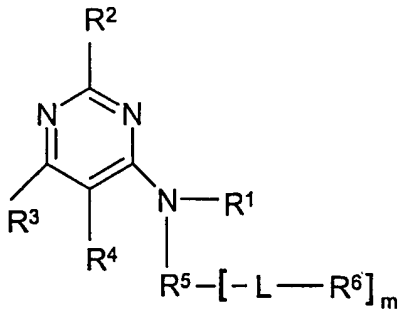
CLAIMS

1. Compounds having the general formula (I)



wherein

R^1 is selected from the group comprising:
–H, linear or branched substituted or unsubstituted C_1–C_6 alkyl, linear or branched C_2–C_6 alkenyl or linear or branched C_2–C_6 alkinyl;

R^2 and **R^4** are independently selected from the group consisting of:
–H, linear or branched substituted or unsubstituted C_1–C_6 alkyl, linear or branched C_2–C_6 alkenyl, linear or branched C_2–C_6 alkinyl, aryl, –F, –Cl, –Br, –I, –CN, $–NH_2$ or $–NO_2$;

R^3 is selected from the group comprising:
–F, –Cl, –Br, –I, substituted or unsubstituted aryl, substituted or unsubstituted –O–aryl, –NH–aryl, –S–aryl, or substituted or unsubstituted –O–heterocyclyl, –NH–heterocyclyl, –S–heterocyclyl, or substituted or unsubstituted –CH=CH–aryl, or substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclyl, or substituted or unsubstituted C_3–C_8 cycloalkyl, or $–NH–(CH_2)_n–X$, wherein n is an integer from 0 to 6 and X is selected from –OH, $–NH_2$ or substituted or unsubstituted C_3–C_8 cycloalkyl;

R^5 is selected from the group consisting of:
substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted C_3–C_8 cycloalkyl, or $–(CH_2)_o–Y$, wherein o is an integer from 0 to 6 and Y represents substituted or unsubstituted aryl, substituted or unsubstituted

heteroaryl, substituted or unsubstituted heterocyclyl or substituted or unsubstituted C_3–C_8 cycloalkyl;

R^6 is selected from the group consisting of:
–H, linear or branched substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted pyrrolidinyl, substituted or unsubstituted C_3–C_8 cycloalkyl, disubstituted cyclohexyl, cyclopentyl, substituted or unsubstituted C_5–C_{12} bicycloalkyl, substituted or unsubstituted adamantyl, $-(CH_2)_q$–group, wherein q is an integer from 1 to 3, under the proviso, if R^6 is selected to be a methylene chain $-(CH_2)_q$–group, R^{17} or R^{19} are selected to be a methylene chain $-(CH_2)_s$–group, wherein s is an integer from 1 to 3 or a $-(CH_2)_t$–A–group, t is an integer from 1 to 3 and A is selected from O or N, respectively, and R^6 and R^{17} or R^6 and R^{19} form together a 5 to 8 membered ring system,
or R^6 represents $-(CH_2)_p$–Z, wherein p is an integer from 0 to 6 and Z is selected from the group comprising:
substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, $-N(R^7R^8)$, wherein R^7 and R^8 represent independently from each other –H, or linear or branched substituted or unsubstituted C_1–C_6 alkyl, or Z is selected from $-(CR^9R^{10}R^{11})$, wherein R^9, R^{10} and R^{11} are independently of each other selected from the group consisting of:
–H, linear or branched substituted or unsubstituted C_1–C_8 alkyl, substituted or unsubstituted aryl or $-N(R^{12}R^{13})$, wherein R^{12} and R^{13} represent independently of each other –H or linear or branched substituted or unsubstituted C_1–C_6 alkyl,
under the proviso, if Z represents $-(CR^9R^{10}R^{11})$ as defined above, p is selected to be an integer from 0 to 6, and
if Z is selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, or $-N(R^7R^8)$ as defined above, p is selected to be an integer from 1 to 6;

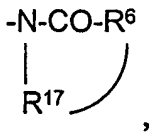
L is selected from the group comprising:
$-NR^{14}$–SO_2–, $-NR^{14}$–SO–,
wherein R^{14} is selected from –H, linear or branched substituted or unsubstituted C_1–C_6 alkyl, $-SO_2$–R^{15} or $-R^{15}$–SO_2–, wherein R^{15} is selected from linear or branched substituted or unsubstituted C_1–C_6

alkyl or C_1–C_6 alkylen, or R^{14} represents $-(CH_2)_r-COOR^{16}$, wherein r is an integer from 0 to 6 and R^{16} is selected from –H or linear or branched substituted or unsubstituted C_1–C_6 alkyl,

$-NR^{17}-CO-$,

wherein R^{17} is selected from –H, linear or branched substituted or unsubstituted C_1–C_6 alkyl, or a $-(CH_2)_s-$group, wherein s is an integer from 1 to 3, and

wherein R^6 and R^{17} represent both a methylene chain group, R^6 and R^{17} may form together a 5 to 8 membered ring system:



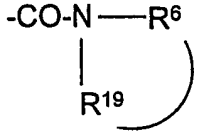
,

$-SO_2-NR^{18}-$,

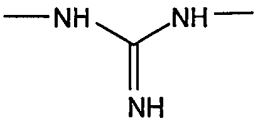
wherein R^{18} is selected from –H, or linear or branched substituted or unsubstituted C_1–C_6 alkyl,

$-CO-NR^{19}-$,

wherein R^{19} is selected from –H, linear or branched substituted or unsubstituted C_1–C_6 alkyl, or a $-(CH_2)_t-A-$ group, wherein t is an integer from 1 to 3 and A is selected from N or O, and wherein if R^6 represents a $-(CH_2)_q-$group and R^{19} represents a $-(CH_2)_t-A-$ group, R^6 and R^{19} may form together a 5 to 8 membered ring system



,

–NH–CO–NH–, –NH–CS–NH–, –NH–CO–O–, 

–CO–, –CO–O–, –SO–, $-SO_2-$, $-SO_3-$ or ;

and **m** is selected to be 0 or 1,

and/or stereoisomeric forms and/or pharmaceutically acceptable salts thereof.

2. The compound according to claim 1, wherein R^5 represents $-(CH_2)_n-R'_3-$, $[-L-R^6]$ represents $-L_m-(R_5)_o$, wherein
wherein each R_1 represents independently R_3, R_5, –H, linear or branched substituted or unsubstituted C_1 – C_6 alkyl, linear or branched C_2– C_6 alkenyl or linear or branched C_2– C_6 alkinyl or adamantyl,
R_2 and R_4 are independently selected from the group consisting of:
R_3, R_5, –H, –CN, $-NH_2$, $-NO_2$, linear or branched substituted or unsubstituted C_1 – C_6 alkyl, linear or branched C_2 – C_6 alkenyl or C_2 – C_6 linear or branched alkinyl;
R_3 and R_3' are independently selected from the group consisting of:
a) halogen, represented by –F, –Cl, –Br or –I,
b) C_3 – C_8 cycloalkyl, which is optionally substituted by at least one of the groups R_6, R'_6, R_7 or R'_7,
c) C_4 – C_{12} bicyclo-alkyl, which is optionally substituted by at least one of the groups R_6, R'_6, R_7 or R'_7,
d) aryl, which is optionally substituted by at least one of the groups R_6, R'_6, R_7 or R'_7,
e) X–aryl, which is optionally substituted by at least one of the groups R_6, R'_6, R_7 or R'_7 and wherein X is independently selected from –O–, –NH–, –S–, linear or branched $-CH_2-(C_2-C_6$ alkyl)-group, linear or branched $-CH_2-(C_2-C_6$ alkenyl)-group, which is optionally substituted by at least one of the groups R_6, R'_6, R_7 or R'_7,
f) partially or fully saturated 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R'_6, R_7 or R'_7; this heterocyclic ring can be fused to another 5 or 6 membered heterocyclic ring, which is optionally substituted by at least one of the groups R_6, R'_6, R_7 or R'_7,
or a 5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R'_6, R_7 or R'_7; this heteroaryl ring can be fused to another partially or fully saturated 5 or 6 membered heterocyclic group, which is optionally substituted by at least one of the groups R_6, R'_6, R_7 or R'_7 or to a 5 or 6 membered heteroaryl ring, which is optionally substituted by at least one of the groups R_6, R'_6, R_7 or R'_7;
g) guanidinyl group, optionally substituted by at least one group R_5 or
h) $-Y-(CH_2)_p-Z$ group, wherein Y represents O, S or NR_5 and Z represents R_5, $-OR_5$, $-N(R_5)_2$ or $-COOR_5$,

R_5 is independently selected from the group consisting of:
– H, R_1, R_2, R_3, R_4, $-(CH_2)_q-COOR_1$, $-CH=CH-COOR_1$,
$-C(R_1)_2N(R_1)_2$, $-(CH_2)_rN(R_1)_2$, $-NR_1-COOR_1$ or $-C(R_1)_3$,

R_6 and R_6' are independently selected from the group consisting of:
R_1, R_2, R_4, R_5, L–H, –H, $-OR_1$, $-N(R_1)_2$, $-C(R_1)_3$, $-CH(R_1)_2$, or $-CH_2R_1$;
R_7 and R'_7 represent independently from each other R_6 and R'_6;

L is selected from the group comprising:
$-NR_5-SO_2-$, $-NR_5-CO-(CH_2)_s-$, –NH–CO–NH–, $-CO-NR_5-$,
$-SO_2-NR_5-$ or –NH–,

m = o is independently selected to be 0 or 1,
n is independently selected to be an integer from 0 to 6,
p, q, r and s are independently from each other an integer from 0 to 6

and/or stereoisomeric forms and/or pharmaceutically acceptable salts thereof.

3. The compound according to claim 1 or 2, wherein R^1 is selected from –H or linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably from –H or linear or branched substituted or unsubstituted C_1–C_4 alkyl more preferably from –H or $-CH_3$, and is most preferably –H.

4. The compound according to claim 1, 2 or 3, wherein R^2 is selected from –H, $-NH_2$ or linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably from –H or linear or branched C_1–C_4 alkyl, and is more preferably –H.

5. The compound according to any one of claims 1 to 4, wherein R^4 is selected from –H, $-NH_2$ or linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably from –H or linear or branched C_1–C_4 alkyl, more preferably from –H or $-CH_3$, and is most preferably –H.

6. The compound according to any one of claims 1 to 5, wherein m is selected to be 0,
R^3 is selected from the group comprising:

Substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, more preferably substituted phenyl, and
wherein R^5 is selected from the group consisting of:
Substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, more preferably substituted phenyl, or $-(CH_2)_o-Y$. wherein o is an integer from 0 to 4 and Y represents substituted or unsubstituted heteroaryl, preferably unsubstituted heteroaryl.

7. The compound according to claim 6, wherein R^3 and R^5 represent phenyl, wherein each phenyl is independently of each other partially or fully substituted with members selected from the group consisting of:
Linear or branched substituted or unsubstituted C_1-C_6 alkyl, preferably linear or branched C_1-C_4 alkyl, more preferably $-CH_3$, linear or branched C_1-C_6 alkoxy, preferably linear or branched C_1-C_4 alkoxy, more preferably $-OCH_3$, $-O-(CH_2)_u-$Phenyl, wherein u is an integer from 0 to 6, preferably from 0 to 4, more preferably from 0 to 2, $-NR^{20}R^{21}$, wherein R^{20} and R^{21} are independently of each other selected from –H or linear or branched C_1-C_6 alkyl, more preferably from –H or linear or branched C_1-C_4 alkyl, and are most preferably –H, $-COOR^{22}$, wherein R^{22} represents linear or branched substituted or unsubstituted C_1-C_6 alkyl, preferably linear or branched C_1-C_4 alkyl, more preferably $-CH_3$, or phenyl is substituted with heteroaryl selected from benzoimidazolyl, benzothiazolyl or benzoxazolyl,
and wherein each phenyl is preferably mono-, di- or trisubstituted, more preferably mono- or disubstituted.

8. The compound according to any one of claims 6 or 7, wherein R^5 represents $-(CH_2)_o-Y$, wherein o is selected to be 2 and wherein Y represents unsubstituted pyridinyl; preferably unsubstituted 4-pyridinyl.

9. The compound according to any one of claims 1 to 5, wherein m is selected to be 1.

10 The compound according to claim 9, wherein R^3 is selected from the group comprising:
–Cl, –Br, –I, preferably –Cl or –Br, more preferably –Cl,
substituted or unsubstituted aryl, substituted or unsubstituted –CH=CH–aryl, preferably substituted or unsubstituted –CH=CH–phenyl, more preferably unsubstituted –CH=CH–phenyl, substituted or

unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, preferably substituted heterocyclyl, substituted or unsubstituted C_3–C_8 cycloalkyl, substituted or unsubstituted W-heterocyclyl, wherein W is selected to be –NH, preferably substituted –NH-heterocyclyl or R^3 represents $-NH-(CH_2)_n-X$, wherein n is an integer from 0 to 4, preferably from 0 to 2, and X is selected from –OH, $-NH_2$ or substituted or unsubstituted C_3–C_8 cycloalkyl, preferably unsubstituted cycloalkyl, more preferably unsubstituted cyclohexyl.

11. The compound according to claim 10, wherein R^3 represents partially or fully substituted heterocyclyl, wherein the heterocyclyl is selected from the group consisting of: Pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, preferably substituted piperazinyl, wherein piperazinyl is N-substituted with linear or branched C_1–C_4 alkyl, preferably $-CH_3$.

12. The compound according to claim 10, wherein R^3 represents substituted or unsubstituted heteroaryl, wherein the heteroaryl is selected from the group consisiting of:
Pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophenyl, furanyl or pyrollyl, preferably pyridinyl, pyrimidinyl, thiophenyl or furanyl, more preferably 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, pyrimidinyl, 2-thiophenyl or 2-furanyl, and wherein the substituted heteroaryl is selected from furanyl, thiophenyl or pyridinyl, preferably 3-pyridinyl or 2-thiophenyl, partially or fully substituted with linear or branched C_1–C_4 alkoxy, preferably with $-OCH_3$, or with $-CO-CH_3$, and wherein the pyridinyl or thiophenyl are preferably monosubstituted.

13. The compound according to claim 10, wherein R^3 represents substituted or unsubstituted phenyl, preferably substituted phenyl.

14. The compound according to claim 13, wherein phenyl is partially or fully substituted with members of the group consisting of:
–F, –Cl, –Br, –I, preferably –F or –Cl, –CN, $-NO_2$,
linear or branched substituted or unsubstituted C_1–C_6 alkyl, preferably linear or branched C_1–C_4 alkyl, linear or branched C_2–C_6 alkenyl, preferably linear or branched C_2–C_4 alkenyl, substituted or unsubstituted phenyl, preferably unsubstituted phenyl,

linear or branched C_1–C_6 alkoxy, preferably linear or branched C_1–C_4 alkoxy,

–O–$(CH_2)_v$–R, wherein v is an integer from 0 to 6, preferably from 0 to 4 and R is selected from the group consisting of:

Phenyl, –O–phenyl, linear or branched C_1–C_4 haloalkyl, heterocyclyl, or –$NR^{23}R^{24}$, wherein R^{23} and R^{24} are independently of each other selected from –H or linear or branched C_1–C_6 alkyl, preferably from –H or linear or branched C_1–C_4 alkyl,

linear or branched C_1–C_6 haloalkyl, preferably linear or branched C_1–C_4 haloalkyl,

linear or branched C_1–C_6 thioalkyl, preferably linear or branched C_1–C_4 thioalkyl,

–$(CH_2)_w$–Q, wherein w is selected to be an integer from 0 to 6, preferably from 0 to 4 and Q is selected from heterocyclyl, –OH, –$NR^{25}R^{26}$, wherein R^{25} and R^{26} are independently of each other selected from –H, linear or branched C_1–C_6 alkyl, preferably –H or linear or branched C_1–C_4 alkyl, or –$(CH_2)_y$–O–CH_3, wherein y is selected to be an integer from 0 to 6, preferably from 0 to 4, or Q represents linear or branched C_1–C_6 alkoxy, preferably linear or branched C_1–C_4 alkoxy,

–$(CH_2)_y$–COR^{27}, wherein y is an integer from 0 to 6, preferably from 0 to 4, and R^{27} is selected from the group comprising:

–H, linear or branched C_1–C_6 alkyl, preferably linear or branched C_1–C_4 alkyl, –OR^{28}, wherein R^{28} is selected from –H or linear or branched C_1–C_6 alkyl, preferably linear or branched C_1–C_4 alkyl, or R^{28} is selected from –$NR^{29}R^{30}$, wherein R^{29} and R^{30} are independently of each other selected from –H, linear or branched C_1–C_6 alkyl or C_3–C_8 cycloalkyl, preferably from –H, linear or branched C_1–C_4 alkyl or C_4–C_6 cycloalkyl,

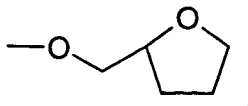
–CH=CH–COOH, –CH=CH–$COOCH_3$ or –NH–T–R^{31}, wherein T is selected from –CO– or –SO_2– and R^{31} represents linear or branched C_1–C_6 alkyl, preferably linear or branched C_1–C_4 alkyl, and

wherein phenyl is mono-, di- or trisubsituted, preferably mono- or disubstituted.

15. The compound according to claim 14, wherein phenyl is substituted with members of the group consisting of:

–F, –Cl, –CN, –C_2H_5, –$CH(CH_3)_2$, –$CH=CH_2$, –OCH_3, –OC_2H_5, –$OCH(CH_3)_2$, –O–Phenyl, –O–CH_2–Phenyl, –O–$(CH_2)_2$–O–Phenyl, –O–$(CH_2)_2$–$N(CH_3)_2$, –O–$(CH_2)_3$–$N(CH_3)_2$, –O–$(CH_2)_3$–NH_2, –OCF_3,

–OH, –CH_2–OH, –CH_2–OCH_3, –SCH_3, –NH_2, –$N(CH_3)_2$, –CH_2–NH_2, –CH_2–$N(CH_3)_2$, –CH=CH–COOH, –CH=CH–$COOCH_3$, –COOH, –$(CH_2)_2$–COOH, –$COOCH_3$, –CF_3, Phenyl, –C(O)–H, –C(O)–CH_3, –C(O)–NH_2, –C(O)–$NHCH(CH_3)_2$, –NH–CO–CH_3, –NH–SO_2–CH_3, –CH_2–$N(CH_3)$–$(CH_2)_2$–O–CH_3,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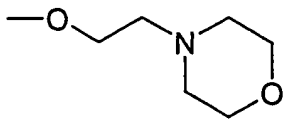
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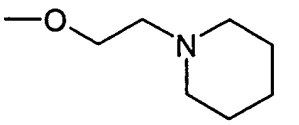
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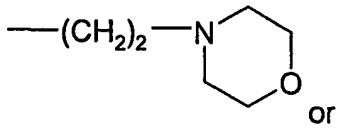
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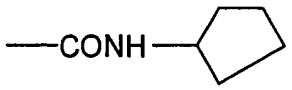
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preferably phenyl is substituted with –OCH_3, –OCH_2–Phenyl, –OH or –NH_2.

16. The compound according to any one of claims 9 – 15, wherein R^5 is selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocyclyl.

17. The compound according to claim 16, wherein R^5 represents substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, more preferably unsubstituted phenyl.

18. The compound according to claim 17, wherein phenyl is partially or fully substituted with linear or branched C_1–C_6 alkyl, preferably with linear or branched C_1–C_4 alkyl, more preferably with –CH_3 or phenyl is partially or fully substituted with –O–$(CH_2)_u$–Phenyl, wherein u is an integer from 0 to 6, preferably from 0 to 4, more preferably from 0 to 2, and is most preferably 1, and wherein phenyl is preferably monosubstituted.

19. The compound according to any one of claims 9 – 18, wherein L is selected from the group comprising:

–NR^{14}–SO_2–,

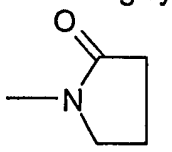
wherein R^{14} is selected from –H, linear or branched C_1–C_4 alkyl, –SO_2–R^{15}– or –R^{15}–SO_2–,

wherein R^{15} is selected from linear or branched substituted or unsubstituted C_1–C_4 alkyl or C_1–C_4 alkylen, or R^{14} represents –

$(CH_2)_r$–$COOR^{16}$, wherein r is an integer from 0 to 4 and R^{16} is selected from –H or linear or branched C_1–C_4 alkyl,

–NR^{17}–CO–,

wherein R^{17} is selected from –H, linear or branched C_1–C_4 alkyl, or a –$(CH_2)_s$–group, wherein s is an integer from 1 to 3, preferably s is selected to be 1, and wherein if R^6 represents a –$(CH_2)_q$–group, wherein q is an integer from 1 to 3, preferably q is selected to be 2 and R^{17} represents a methylene chain –$(CH_2)_s$–group, R^6 and R^{17} may form together a 5 to 8 membered ring system, preferably R^6 and R^{17} form together a 5 membered ring system



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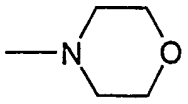
–SO_2–NR^{18}–,

wherein R^{18} is selected from –H or linear or branched C_1–C_4 alkyl,

–CO–NR^{19}–,

wherein R^{19} is selected from –H, linear or branched C_1–C_4 alkyl, or a –$(CH_2)_t$–A– group, wherein t is an integer from 1 to 3 and A is selected from N or O, and wherein if R^6 represents a –$(CH_2)_q$–group wherein q is an integer from 1 to 3, preferably q is selected to be 2 and R^{19} represents a –$(CH_2)_t$–A– group, wherein t is selected to be 2 and A represents O, R^6 and R^{19} may form together a 6-membered ring system



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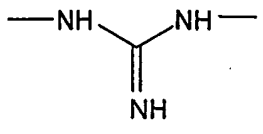
–NH–CO–NH–, –SO_2– or 

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and if R^5 represents phenyl, L is preferably in meta- or para-position of the phenyl.

20. The compound according to claim 19, wherein L is selected from the group consisting of:
$-NR^{14}-SO_2-$,
wherein R^{14} is selected from –H, $-(CH_2)_2-CH_3$,
$-SO_2-R^{15}$, wherein R^{15} represents $-(CH_2)_2-CH_3$,
or $-(CH_2)_r-COOR^{16}$, wherein r is selected to be an integer from 0 to 2, and is preferably 1, and R^{16} represents $-CH_3$,

$-NR^{17}-CO-$, $-SO_2-NR^{18}-$, $-CO-NR^{19}-$,
wherein R^{17}, R^{18} and R^{19} represent –H,
–NH–CO–NH– or $-SO_2-$,
preferably L is selected from $-NH-SO_2-$, –NH–CO–, –CO–NH–, $-SO_2-NH-$, –NH–CO–NH– or $-SO_2-$.

21. The compound according to any one of claims 9 to 20, wherein $\mathbf{R^6}$ is selected from the group comprising:
–H, linear or branched C_1-C_8 alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted pyrrolidinyl, substituted or unsubstituted C_3-C_8 cycloalkyl, disubstituted cyclohexyl, cyclopentyl, substituted or unsubstituted C_5-C_{12} bicycloalkyl, substituted or unsubstituted adamantyl, or $-(CH_2)_p-Z$, wherein p is an integer from 0 to 4 and Z is selected from the group comprising:
substituted or unsubstituted aryl, preferably unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, $-N(R^7R^8)$, wherein R^7 and R^8 represent independently from each other –H, or linear or branched C_1-C_6 alkyl, or Z represents $-(CR^9R^{10}R^{11})$, wherein R^9, R^{10} and R^{11} are independently of each other selected from the group consisting of: –H, linear or branched C_1-C_4 alkyl, substituted or unsubstituted aryl or $-N(R^{12}R^{13})$, wherein R^{12} and R^{13} represent independently of each other –H or linear or branched C_1-C_4 alkyl, and wherein if Z is selected from substituted or unsubstituted aryl, preferably unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, p can not be selected to be 0.

22. The compound according to claim 21, wherein $\mathbf{R^6}$ is selected from the group consisting of:

–H, linear or branched C_1–C_6 alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted C_3–C_8 cycloalkyl, unsubstituted C_5–C_{12} bicycloalkyl, preferably unsubstituted bicyclo[2.2.1] heptanyl, unsubstituted adamantyl or $-(CH_2)_p-Z$, wherein p is an integer from 0 to 2 and Z is selected from the group comprising:
substituted or unsubstituted phenyl, substituted or unsubstituted heterocyclyl, $-N(R^7R^8)$, wherein R^7 and R^8 represent independently from each other –H, or linear or branched C_1–C_4 alkyl, or Z represents $-(CR^9R^{10}R^{11})$, wherein R^9, R^{10} and R^{11} are independently of each other selected from the group consisting of: –H, linear or branched C_1–C_6 alkyl, unsubstituted aryl or $-N(R^{12}R^{13})$, wherein R^{12} and R^{13} represent independently of each other –H or linear or branched C_1–C_4 alkyl.

23. The compound according to claim 22, wherein R^6 represents –H or linear or branched C_1–C_6 alkyl, preferably –H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C(CH_3)_3$ or $-CH_2-C(CH_3)_3$, more preferably –H, $-CH_3$ or $-C(CH_3)_3$.

24. The compound according to claim 22, wherein R^6 represents substituted or unsubstituted aryl, such as substituted or unsubstituted phenyl or naphtyl, wherein if R^6 represents substituted naphthyl, napthyl is partially or fully substituted with –OH or linear or branched C_1–C_4 alkoxy, preferably –OH and wherein napthyl is preferably monosubstituted,
or wherein if R^6 represents substituted phenyl, phenyl is partially or fully substituted with members of the group comprising:
Phenyl, linear or branched C_1–C_6 alkyl, preferably linear or branched C_1–C_4 alkyl, more preferably $-CH_3$, $-C_3H_7$, $-CH(CH_3)_2$ or $-C(CH_3)_3$, substituted or unsubstituted heterocyclyl, preferably unsubstituted morpholinyl or N-substituted piperazinyl, wherein N-substituted piperazinyl is substituted with linear or branched C_1–C_4 alkyl, preferably with $-CH_3$, or phenyl is partially or fully substituted with –OH or $-N(R^{32}R^{33})$, wherein R^{32} and R^{33} represent independently of each other –H or linear or branched C_1–C_4 alkyl, preferably –H or $-CH_3$, more preferably –H.

25. The compound according to claim 22, wherein R^6 represents substituted or unsubstituted heteroaryl, wherein the **heteroaryl** is selected from the group comprising:

Pyrrolyl, thiophenyl, furanyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothioazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyradizinyl, tetrahydroquinolinyl, quinolinyl, isoquinolinyl, benzoimidazolyl, benzothiazolyl, benzooxazolyl, benzo[1,3]dioxolyl, indolyl, benzofuranyl, benzothiophenyl, indazolyl or chrom-2-onyl,
preferably R^6 is selected from the group consisting of:
imidazolyl, wherein preferably one N-atom of the imidazolyl, is substituted with linear or branched C_1-C_4 alkyl, more preferably with $-CH_3$,
pyridinyl, preferably 4-pyridinyl, tetrahydroquinolinyl, quinolinyl, benzoimidazolyl, benzothiazolyl, benzo[1,3]dioxolyl, indolyl, indazolyl or chromen-2-onyl.

26. The compound according to claim 22, wherein R^6 represents substituted or unsubstituted heterocyclyl, wherein heterocyclyl is selected from the group comprising:
aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl,
preferably R^6 is selected from azetidinyl, pyrrolidinyl, preferably 2-pyrrolidinyl or 2-piperidinyl, 3-piperidinyl or 4-piperidinyl, preferably 2-piperidinyl.

27. The compound according to claim 26, wherein R^6 represents partially or fully substituted heterocyclyl, preferably partially or fully substituted piperidinyl, more preferably N-substituted piperidinyl, substituted with linear or branched C_1–C_4 alkyl, preferably $-CH_3$, or $-N-COOR^{34}$, wherein R^{34} represents –H or linear or branched C_1–C_4 alkyl, preferably $-(CCH_3)_3$.

28. The compound according to claim 22, wherein R^6 represents substituted or unsubstituted C_3–C_8 cycloalkyl, preferably substituted or unsubstituted cyclopentyl or cyclohexyl, and wherein cyclopentyl or cyclohexyl are partially or fully substituted with linear or branched C_1–C_6 alkyl, –OH, $-NH_2$ or $-NH-COOR^{35}$, wherein R^{35} represents –H or linear or branched C_1–C_6 alkyl, preferably linear or branched C_1–C_4 alkyl, more preferably $-C(CH_3)_3$, and wherein cyclopentyl or cyclohexyl are preferably substituted with $-NH_2$, and wherein cyclopentyl or cyclohexyl are preferably mono-, di- or trisubstituted, more preferably monosubstituted.

29. The compound according to claim 22, wherein R^6 represents $-(CH_2)_p-Z$, wherein p is selected to be 1 or 2 and Z is selected from the group comprising:
Substituted or unsubstituted phenyl, wherein in case phenyl is substituted, it is substituted with linear or branched C_1-C_4 alkyl, preferably $-CH_3$,
substituted or unsubstituted heterocyclyl, preferably substituted or unsubstiuted piperidinyl, more preferably N-substituted or unsubstituted 2-piperidinyl, wherein in case 2-piperidinyl is N-substituted, it is substituted with $-COOR^{36}$, wherein R^{36} represents linear or branched C_1-C_6 alkyl, preferably linear or branched C_1-C_4 alkyl, more preferably $-C(CH_3)_3$, or Z represents $-N(R^7R^8)$, wherein R^7 and R^8 represent independently of each other –H, or linear or branched C_1-C_4 alkyl, preferably –H, $-CH_3$ or $-C_2H_5$,
or R^6 represents $-(CH_2)_p-Z$, wherein p is selected to be an integer from 0 to 2 and Z is selected to be $-(CR^9R^{10}R^{11})$, wherein R^9, R^{10} and R^{11} are independently of each other selected from the group consisting of:
–H, linear or branched C_1-C_5 alkyl, preferably $-CH_3$, $-CH(CH_3)_2$, or $-CH(CH_3)-C_2H_5$, substituted or unsubstituted aryl, or $-N(R^{12}R^{13})$, wherein R^{12} and R^{13} represent independently of each other –H or linear or branched C_1-C_4 alkyl, preferably –H or $-CH_3$.

30. The compound according to any one of claims 9 - 29, wherein m is selected to be 1, R^1, R^2 and R^4 represent –H, R^3 represents monosubstituted phenyl, R^5 represents monosubstituted or unsubstituted phenyl, L is selected from the group comprising:
$-NH-CO-$, $-NH-SO_2-$, $-SO_2-NH-$, $-CO-NH-$ or $-SO_2-$, and
R^6 is selected from the group consisting of:
–H, linear or branched C_1-C_4 alkyl, monosubstituted phenyl,
substituted or unsubstituted heterocyclyl, wherein heterocyclyl is preferably selected from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl, substituted or unsubstituted heteroaryl, wherein heteroaryl is selected from imidazolyl, pyridinyl, tetrahydroquinolinyl, quinolinyl, benzoimidazolyl, benzothiazolyl, benzo[1,3]dioxolyl, indolyl, indazolyl or chromen-2-only or R^6 represents substituted or unsubstituted C_3-C_8 cycloalkyl.

31. The compound according to any one of claims 1 to 30, wherein the compound represents a chiral compound.

32. The compound according to claim 31, wherein the compound represents a racemate, or a S or a R enantiomer or a mixture of isomers.

33. The compound according to any one of claims 1 to 32, wherein the compound is selected from the group of compounds consisting of:

Compound 1: *N*-{4-[6-(4-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-4-methyl-benzenesulfonamide,

Compound 2: *N*-{4-[6-(3-Methoxy-phenyl)-pyrimidin-4ylamino]-phenyl}-4-methyl-benzenesulfonamide,

Compound 3: *N*-{5-[6-(4-Methoxy-phenyl)-pyrimidin-4ylamino]-2-methyl-phenyl}-methanesulfonamide,

Compound 4: 4-Amino-*N*-{4-[6-(2-benzyloxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 5: *N*-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4ylamino]-phenyl}-4-methyl-benzenesulfonamide,

Compound 6: 4-Amino-*N*-{4-[6-(4-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 7: [6-(2-Benzyloxy-phenyl)-pyrimidin-4-yl]-(2-pyridin-4-yl-ethyl)-amine,

Compound 8: 4-Amino-*N*-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 9: 1-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-pyrrolidin-2-one,

Compound 10: *N*-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-acetamide,

Compound 11: *N*-{4-[6-(4-Hydroxy-phenyl)-pyrimidin-4ylamino]-phenyl}-4-methyl-benzenesulfonamide,

Compound 12: *N*-{5-[6-(3-Amino-phenyl)-pyrimidin-4ylamino]-2-methyl-phenyl}-methanesulfonamide,

Compound 13: [6-(3-Amino-phenyl)-pyrimidin-4-y]-(2-pyridin-4-yl-ethyl)-amine,

Compound 14: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]l-benzamide,

Compound 15: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]l-benzoic acid methyl ester,

Compound 16: 4-Amino-*N*-{4-[6-(4-hydroxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 17: 3-(4-{6-[4-Toluene-4-sulfonylamino)-phenylamino]-pyrimidin-4-yl}-phenyl)-propionic acid,

Compound 18: *N*-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4ylamino]-phenyl}-4-methyl- *N* –propyl-benzenesulfonamide,

Compound 19: *N*-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2,2-dimethyl-propionamide,

Compound 20: 2-Amino-*N*-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 21: 4-Amino-*N*-{4-[6-(3-amino-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 22: N-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-benzene-1,4-diamine,

Compound 23: 4-Isopropyl-*N*-{4-[6-(2-methoxy-phenyl)-pyrimidin-4ylamino]-phenyl}-benzenesulfonamide,

Compound 24: *N*-[4-*(*6 -Chloro-pyrimidin-4ylamino)-phenyl]-4-methyl-benzenesulfonamide,

Compound 25: 4-Amino-*N*-[4-*(6* -chloro-pyrimidin-4ylamino)-phenyl]-benzamide,

Compound 26: *N*-[6-(2-Methox-phenyl)-pyrimidin-4-ylamino]-*N*-methyl-benzene-1,4-diamine,

Compound 27: [{4-[6-(4-Hydox-phenyl)-pyrimidin-4-ylamino]-phenyl}-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester,

Compound 28: [{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester,

Compound 29: **(*S*)**-2-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenylcarbamoyl}-piperidine-1-carboxylic acid *tert*-butyl ester,

Compound 30: **(*S*)**-Piperidine-2-carboxylic acid *N*-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide

Compound 31: 4-Amino-*N*-{4-[6-(2,4-dimethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 32: 4-Amino-*N*-{4-[6-styryl-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 33: *N*-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4yl-amino]-phenyl}-methanesulfon-amide,

Compound 34: Biphenyl-4-sulfonic acid -{4-[6-(2-methoxy-phenyl)-pyrimidin-4ylamino]-phenyl}-amide,

Compound 35: 4-Amino-*N*-{4-[6-(5-isopropyl-2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 36: Bicyclo[2.2.1)heptane-2-carboxylic acid {4-[6-(2-methoxyphenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 37: *N*-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-3-methyl-2-phenyl-butyramide,

Compound 38: 1-Cyclohexyl-3-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-urea,

Compound 39: 4-Amino-*N*-{4-[6-(5-chloro-2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 40: E-3-(3-{6-[4-(Toluene-4-sulfonylamino)-phenylamino]-pyrimidin-4-yl}-phenyl)-acrylic acid,

Compound 41: Cyclohexanecarboxylic acid {4-[6-(2-methoxy phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 42: *N*-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-3,3-dimethyl-butyramide,

Compound 43: 4-Amino-*N*-{4-[6-(cyclohexylmethyl-amino)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 44: *N*-Cyclohexyl-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 45: 4-*tert*-Butyl-*N*-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 46: 2-Dimethylamino-*N*-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-acetamide,

Compound 47: (1-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl-carbamoyl-cyclopentyl)-carbamic acid *tert* butyl ester

Compound 48: 2-({4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenylcarbamoyl}-methyl) piperidine-1-carboxylic acid *tert*-butyl ester,

Compound 49: *N*-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-4-(4-methyl-piperazin-1-yl)-benzamide,

Compound 50: *N*-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-isonicotinamide,

Compound 51: 4-Amino-*N*-{4-[6-(2,6-dimethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 52: {4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-*N*-phenyl-benzamide,

Compound 53: *N*-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-guanidine,

Compound 54: N-*tert*-Butyl-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 55: 4-Amino-*N*-{4-[6-(2-ethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 56: 4-Amino-*N*-{4-[6-(2,3-dimethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 57: 4-Amino-*N*-{4-[6-(2,5-dimethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 58: 4-Amino-*N*-{4-[6-(2-isopropoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 59: *N*-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2-piperidine-2-yl-acetamide,

Compound 60: 4-Amino-*N*--{4-[6-(2-hydroxy-ethylamino)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 61: Adamantane-1-carboxylic acid-{4-[6-(2-methoxyphenyl)-pyrimidin-4-yl-amino]-phenyl}-amide,

Compound 62: (4-Benzoxazol-2-yl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 63: [4-(1*H*-Benzimidazole-2-yl)-phenyl]-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 64: 3-Diethylamino-*N*-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-propion amide,

Compound 65: (***S***)-1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]phenyl}amide,

Compound 66: 1-Amino-cyclohexane carboxylic acid-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 67: 4-Amino-*N*-[4-(6-pyridin-4-yl-pyrimidin-4-ylamino)-phenyl]-benzamide,

Compound 68: 1-Amino-cyclopentanecarboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 69: (***R***)-Piperidine-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 70: 1-Methyl-4*H*-imidazole-4-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 71: *N*-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2-phenyl-actetamide,

Compound 72: *N*- [4-(6-Chloro-pyrimidin-4-ylamino)-phenyl]-2,2-dimethyl-propionamide,

Compound 73: 2,2-Dimethyl-*N*-[4-(6-pyridin-3-yl-pyrimidin-4-ylamino)-phenyl]- -propionamide,

Compound 74: 2,2-Dimethyl-*N*-{4-[6-(1-methyl-piperidin-4-ylamino)-pyrimidin-4-ylamino]-phenyl}-propionamide,

Compound 75: 3-{6-[4-(2,2-Dimethyl-propionylamino)-phenylamino]-pyrimidin-4-yl}-benzoic acid,

Compound 76: 4-Amino-*N*-[4-(6-phenyl-pyrimidin-4-ylamino)-phenyl]-benzamide,

Compound 77: 4-Amino-*N*-[4-(6-thiophen-2-yl-pyrimidin-4-ylamino)-phenyl]-benzamide

Compound 78: 2,2-Dimethyl-*N*-{4-[6-(4-methyl-piperazin-1-ylamino)-pyrimidin-4-ylamino]-phenyl}-propionamide,

Compound 79: *N*-{4-[6-(2-Amino-ethylamino)-pyrimidin-4-ylamino]-phenyl}-2,2-dimethyl-propionamide,

Compound 80: *N*-{4-[6-(3-Hydroxy-propylamino)-pyrimidin-4-ylamino]-phenyl}-2,2-dimethyl-propionamide,

Compound 81: **(*S*)**-2-Amino-*N*- {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2-phenyl-acetamide,

Compound 82: **(*S*)**-*N*- {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2-methylamino-2-phenyl-acetamide,

Compound 83: ***(R,R)/(SS)*-*N*-(2-Amino-cyclohexyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 84: Benzothiazole- 2-carboxylic acid -{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 85: *N*-{4-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-phenyl}- 2,2-dimethyl -propionamide,

Compound 86: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-*N*-piperidin-3-yl-benzamide.

Compound 87: 1-Methyl-piperidine-3-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide.

Compound 88: 4-(6-Chloro-pyrimidin-4-ylamino)-*N*-cyclohexyl-benzamide,

Compound 89: 1-Methyl-piperidine-4-carobxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amino]-phenyl}-amide,

Compound 90: **(S)**-Azetidine-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amino]-phenyl}-amide,

Compound 91: (R)-Pyrrolidine-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amino]-phenyl}-amide,

Compound 92: [6-(4-Methoxy-phenyl)-pyrimidin-4-yl]-(2-pyridin-4-yl-ethyl)-amine,

Compound 93: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(2-pyridin-4-yl-ethyl)-amine,

Compound 94: 2-[6-(2-Pyridin-4-yl-ethylamino)-pyrimidin-4-yl]-phenol,

Compound 95: 4-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 96: N-(4-{[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-methyl-amino}-phenyl)-4-methyl-benzenesulfonamide,

Compound 97: 4-Amino-N-{4-[2-amino-6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 98: Quinoline-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 99: 6-(2-Isopropoxy-phenyl)-pyrimidin-4-yl]-(2-pyridin-4-yl-ethyl)-amine,

Compound 100: N-{5-[6-(3-Methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane sulfonamide,

Compound 101: 2-Dimethylamino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2-phenyl-acetamide,

Compound 102: 3-Amino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-propion- amide,

Compound 103: 4-Amino-N-(4-{6-[2-(3-amino-propoxy)-phenyl]-pyrimidin-4-ylamino}-phenyl)-benzamide,

Compound 104: N-{3-[6-(3-Methanesulfonylamino-4-methyl-phenylamino)-pyrimidin-4-yl]-phenyl}-acetamide,

Compound 105: N-{5-[6-(3-Hydroxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}methane-sulfonamide,

Compound 106: N-[2-Methyl-5-(6-phenyl-pyrimidin-4-ylamino)-phenyl]-methanesulfonamide,

Compound 107: N-{2-Methyl-5-[6-(3-trifluoromethyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-methanesulfonamide,

Compound 108: N-{5-[6-(3-Methanesulfonylamino-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methanesulfonamide,

Compound 109: N-{5-[6-(3-Amino-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-benzene-sulfonamide,

Compound 110: N-[5-([4,5']Bipyrimidinyl-6-ylamino)-2-methyl-phenyl]-methanesulfonamide,

Compound 111: 1-Benzo[1,3]dioxol-5-yl-3-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-urea,

Compound 112: 1-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-3-(4-methyl-benzyl)-urea,

Compound 113: 1-tert-Butyl-3-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-urea,

Compound 114: 2,2-Dimethyl-N-{4-[6-(2-trifluoromethyl-phenyl)-pyrimidin-4-ylamino]-phenyl} –propionamide,

Compound 115: 3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 116: Propane-1-sulfonic acid {5-[6-(3-amino-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-amide,

Compound 117: 4-[6-(3-Amino-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 118: N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2-methyl-2-methylamino-propionamide,

Compound 119: N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-3-methyl-phenyl}-2,2-dimethyl-propionamide,

Compound 120: N-{5-[6-(3-Amino-phenyl)-pyrimidin-4-ylamino]-2-benzyloxy-phenyl}-methanesulfonamide,

Compound 121: N-{3-[6-(3-Amino-phenyl)-pyrimidin-4-ylamino]-phenyl}-methanesulfon-amide,

Compound 122: N-{3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2,2-dimethyl-propionamide,

Compound 123: N*1*-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-2-methyl-benzene-1,4-diamine,

Compound 124: N-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-benzene-1,3-diamine,

Compound 125: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N-(4-morpholin-4-yl-phenyl)-benzamide,

Compound 126: 2,2-Dimethyl-N-{4-[6-(2-vinyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-propionamide,

Compound 127: N-{4-[6-(2-Fluoro-phenyl)-pyrimidin-4-ylamino]-phenyl}-2,2-dimethyl-propionamide,

Compound 128: (S)-Piperidine-2-carboxylic acid {3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 129: 2-Oxo-2H-chromene-3-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 130: Benzo[1,3]dioxole-5-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 131: N-{4-[6-(2-Ethyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-2,2-dimethyl-propion-amide,

Compound 132: N-[4-(6-Biphenyl-2-yl-pyrimidin-4-ylamino)-phenyl]-2,2-dimethyl-propion-amide,

Compound 133: 1H-Indole-3-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 135: N-((1R,2R) / (1S,2S)-2-Hydroxy-cyclohexyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 136: N-(4-Hydroxy-phenyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 137: N-(4-Isopropyl-phenyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 138: 1H-Benzoimidazole-5-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 139: 1-Hydroxy-naphthalene-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 140: (2S,3S)-2-Amino-3-methyl-pentanoic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 141: 1H-Indazole-3-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 142: Quinoline-8-sulfonic acid {5-[6-(3-amino-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-amide,

Compound 143: (S)-2-Amino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-3-methyl-butyramide,

Compound 144: 1-Methyl-1H-imidazole-4-sulfonic acid {5-[6-(3-amino-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-amide,

Compound 145: 3-Hydroxy-naphthalene-2-carboxylic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 146: 2-Amino-N-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-2-naphthalen-2-yl-acetamide,

Compound 147: {4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-morpholin-4-yl-methanone,

Compound 148: N-((1S,2R) / (1R,2S)-2-Amino-cyclohexyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 149: 4-Amino-N-{4-[6-(2-methoxy-phenyl)-5-methyl-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 150: 3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 151: 4-Amino-N-{4-[6-(2-hydroxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 152: N-[6-(2-Methoxy-phenyl)-5-methyl-pyrimidin-4-yl]-benzene-1,4-diamine,

Compound 153: Propane-2-sulfonic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 154: Propane-1-sulfonic acid {4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 155: N-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-benzene sulfonamide,

Compound 156: N-{5-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methanesulfonamide,

Compound 157: N-{5-[6-(3-Dimethylamino-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methanesulfonamide,

Compound 158: N-{5-[6-(2-Isopropoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methanesulfonamide,

Compound 159: N-Bis-propane-1-sulfonic acid-{4- [6-(2-methoxy-phenyl)-5-methyl-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 160: Propane-1-sulfonic acid {4-[6-(2-methoxy-phenyl)-5-methyl-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 161: N-(2-Amino-cyclohexyl)-4-[6-(4-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 162: N-{5-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methanesulfonamide,

Compound 163: N-{5-[6-(3-Cyano-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane sulfonamide,

Compound 164: (S)-Piperidine-2-carboxylic acid {3-[6-(2-benzyloxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 165: N-{5-[6-(3-Formyl-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane sulfonamide,

Compound 166: N-{5-[6-(2-Hydroxymethyl-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methanesulfonamide,

Compound 167: (S)-Piperidine-2-carboxylic acid {3-[6-(4-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 168: (S)-Piperidine-2-carboxylic acid {3-[6-(3-formyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 169: (S)-Piperidine-2-carboxylic acid {3-[6-(3-dimethylamino-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 170: (S)-Piperidine-2-carboxylic acid {3-[6-(2-hydroxymethyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 171: (S)-Piperidine-2-carboxylic acid {3-[6-(2-methoxy-pyridin-3-yl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 172: (S)-Piperidine-2-carboxylic acid {3-[6-(6-methoxy-pyridin-3-yl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 173: (S)-Piperidine-2-carboxylic acid {3-[6-(4-benzyloxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 174: (S)-Piperidine-2-carboxylic acid {3-[6-(4-phenoxy-phenyl)-pyrimidin-4-yl-amino]-phenyl}-amide

Compound 175: N-{5-[6-(4-Hydroxymethyl-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methanesulfonamide, and

Compound 176: N-{5-[6-(2-Methoxy-pyridin-3-yl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methanesulfonamide.

Compound 177: (S)-Piperidine-2-carboxylic acid {4-[6-(4-acetylamino-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 178: (S)-Piperidine-2-carboxylic acid {4-[6-(3-methanesulfonylamino-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 179: (S)-Piperidine-2-carboxylic acid {4-[6-(3-acetyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 180: (S)-Piperidine-2-carboxylic acid {4-[6-(4-cyclopentylcarbamoyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 181: N-{5-[6-(2-Hydroxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methanesulfonamide,

Compound 182: (E)-3-{3-[6-(3-Methanesulfonylamino-4-methyl-phenylamino)-pyrimidin-4-yl]-phenyl}-acrylic acid methyl ester,

Compound 183: N-{5-[6-(3-Hydroxymethyl-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methanesulfonamide,

Compound 184: N-Butyl-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 185: (3-Methanesulfonyl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 186: (S)-Piperidine-2-carboxylic acid {4-[6-(2,3-dimethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 187: (S)-Piperidine-2-carboxylic acid {4-[6-(2,4-dimethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 188: (S)-Piperidine-2-carboxylic acid {4-[6-(2-isopropoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 189: (S)-Piperidine-2-carboxylic acid {4-[6-(2-methylsulfanyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 190: (S)-Piperidine-2-carboxylic acid {4-[6-(2-trifluoromethoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 191: (S)-Piperidine-2-carboxylic acid {4-[6-(5-acetyl-thiophen-2-yl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 192: (S)-Piperidine-2-carboxylic acid {4-[6-(2-chloro-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 193: (S)-Piperidine-2-carboxylic acid {4-[6-(3-hydroxymethyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 194: N-((1S,2S) / (1R,2R)-2-Amino-cyclohexyl)-4-[6-(3-hydroxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 195: N-((1S,2S) / (1R,2R)-2-Amino-cyclohexyl)-4-[6-(3-methanesulfonyl-amino-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 196: 4-[6-(2-Acetylamino-phenyl)-pyrimidin-4-ylamino]-N-((1S,2S) / (1R,2R)-2-amino-cyclohexyl)-benzamide,

Compound 197: N-{5-[6-(2-Methoxymethyl-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-methane-sulfonamide,

Compound 198: N-((1R,2R)/(1S,2S)-2-Amino-cyclohexyl)-4-[6-(2-benzyloxy-phenyl)-pyrimidin-4-yl-amino]-benzamide,

Compound 199: N-((1R,2R)/(1S,2S)-2-Amino-cyclohex-yl)-4-[6-(2-isopropoxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 200: 4-Amino-N-{4-[6-(4-methoxy-phenyl)-5-methyl-pyrimidin-4-ylamino]-phenyl}-benzamide,

Compound 201: 3-{6-[4-((1R,2R)/(1S,2S)-2-Amino-cyclohexylcarbamoyl)-phenylamino]-pyrimidin-4-yl}-benzoic acid methyl ester,

Compound 202: (S)-Piperidine-2-carboxylic acid {4-[6-(4-methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 203: (S)-Piperidine-2-carboxylic acid {4-[6-(3-methoxymethyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 204: N-[6-(2-Methoxy-phenyl)-2-methyl-pyrimidin-4-yl]-benzene-1,4-diamine,

Compound 205: N-[6-(4-Methoxy-phenyl)-2-methyl-pyrimidin-4-yl]-benzene-1,4-diamine,

Compound 206: N-((1R,2R)/(1S,2S)-2-Amino-cyclohexyl)-4-[6-(3-amino-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 207: 4-[6-(3-Acetylamino-phenyl)-pyrimidin-4-ylamino]-N-((1R,2R)/(1S,2S)-2-amino-cyclohexyl)-benzamide,

Compound 208: N-((1R,2R)/(1S,2S)-2-Amino-cyclohexyl)-4-[6-(4-benzyloxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 209: N-((1R,2R)/(1S,2S)-2-Amino-cyclohexyl)-4-[6-(3-cyano-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 210: N-((1R,2R)/(1S,2S)-2-Amino-cyclohexyl)-4-[6-(2-methoxymethyl-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 211: (S)-Piperidine-2-carboxylic acid {4-[6-(3-dimethylaminomethyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 212: N-((1R,2R)/(1S,2S)-2-Amino-cyclohexyl)-4-(6-quinolin-3-yl-pyrimidin-4-ylamino)-benzamide,

Compound 213: N-((1R,2R)/(1S,2S)-2-Amino-cyclohexyl)-4-(2'-methoxy-[4,5']bipyrimidinyl-6-ylamino)-benzamide,

Compound 214: 3-[6-(3-Amino-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 215: 3-[6-(4-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 216: (R,R)-N-(2-Amino-cyclohexyl)-4-[6-(2-hydroxymethyl-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 217: N-(2-Diethylamino-ethyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 218: (R,R)-N-(2-Amino-cyclohexyl)-4-[6-(2-hydroxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 219: (R,R)-N-(2-Amino-cyclohexyl)-4-[6-(2-methoxy-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide,

Compound 220: (R,R)-N-(2-Amino-cyclohexyl)-4-[6-(5-dimethylaminomethyl-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide,

Compound 221: (R,R)-5-{6-[4-(2-Amino-cyclohexylcarbamoyl)-phenylamino]-pyrimidin-4-yl}-pyridine-2-carboxylic acid dimethylamide,

Compound 222: (R,R)-N-(2-Amino-cyclohexyl)-4-[6-(6-methylsulfanyl-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide,

Compound 223: (R,R)-N-(2-Amino-cyclohexyl)-4-[6-(5-aminomethyl-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide,

Compound 224: (R,R)-N-(2-Amino-cyclohexyl)-4-[6-(4-methylsulfanyl-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide,

Compound 225: N-(2-Amino-cyclohexyl)-4-[6-(5-hydroxymethyl-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide,

Compound 226: rac-4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N-pyrrolidin-3-yl-benzamide,

Compound 227: (R,R)-N-(2-Amino-cyclohexyl)-4-[6-(5-dimethyamino-pyridin-3-yl)-pyrimidin-4-ylamino]-benzamide,

Compound 228: (R,R)-4-[6-(5-Acetyl-thiophen-2-yl)-pyrimidin-4-ylamino]-N-(2-amino-cyclohexyl)-benzamide,

Compound 229: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[3-(piperidine-1-sulfonyl)-phenyl]-amine N-(2-diethylamino-ethyl)-benzamide,

Compound 230: (R,R)-4-[6-(2-Acetyl-phenyl)-pyrimidin-4-ylamino]-N-(2-amino-cyclohexyl)-benzamide,

Compound 231: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N-pyridin-3-yl-benzamide,

Compound 232: N-(1-Acetyl-piperidin-3-yl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 233: (R,R)-N-(2-Amino-cyclohexyl)-4-[6-(2-dimethylamino-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 234: 4-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzoylamino}-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester,

Compound 235: 2-Chloro-5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 236: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[3-(piperidine-1-sulfonyl)-phenyl]-amine,

Compound 237: N-Allyl-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 238: N-Benzyl-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 239: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[3-(pyrrolidine-1-sulfonyl)-phenyl]-amine,

Compound 240: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[3-(morpholine-4-sulfonyl)-phenyl]-amine,

Compound 241: 3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide,

Compound 242: N-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-N-(3-sulfamoyl-phenyl)-acetamide,

Compound 243: N,N-Diallyl-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 244: 3-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 245: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[4-(4-nitro-benzenesulfonyl)-phenyl]-amine,

Compound 246: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-trifluoromethanesulfonyl-phenyl)-amine,

Compound 247: (4-Methanesulfonyl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 248: N-(3,4-Dimethyl-isoxazol-5-yl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 249: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N-propyl-benzenesulfonamide,

Compound 250: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 251: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-N,N-dimethyl-benzenesulfonamide,

Compound 252: N-(2-Methoxy-ethyl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 253: [6-(2-Benzyloxy-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine,

Compound 254: 2-[6-(3-Methanesulfonyl-phenylamino)-pyrimidin-4-yl]-phenol,

Compound 255: [6-(3-Amino-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine,

Compound 256: 5-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-benzenesulfonic acid,

Compound 257: 2-{3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonyl}-ethanol,

Compound 258: (2-Fluoro-5-methanesulfonyl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 259: [6-(2-Amino-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine,

Compound 260: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(3-trifluoromethanesulfonyl-phenyl)-amine,

Compound 261: (3-Methanesulfonyl-phenyl)-[6-(2-Phenoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 262: [6-(2-Butoxy-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine,

Compound 263: (3-Ethenesulfonyl-phenyl-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 264: (S)-Piperidine-2-carboxylic acid {4-[6-(4-methylsulfanyl-phenyl)-pyrimidin-4-ylamino]-phenyl}-amide,

Compound 265: 2-Chloro-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzoic acid methyl ester,

Compound 266: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-phenoxy-benzyl)-amine,

Compound 267: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-3-methyl-benzoic acid methyl ester,

Compound 268: [6-(3-Amino-phenyl)-pyrimidin-4-yl]-(1-methanesulfonyl-2,3-dihydro-1*H*-indol-6-yl)-amine,

Compound 269: 3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester,

Compound 270: {4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-acetic acid,

Compound 271: (1*H*-Indazol-6-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 272: 1-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-butan-1-one,

Compound 273: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-piperidin-3-yl-amine,

Compound 274: {4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-phenyl-methanone,

Compound 275: *N*-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-*N'*-phenyl-benzene-1,3-diamine,

Compound 276: (3-[1,3]Dioxan-2-yl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 277: (3-Methoxy-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 278: (4-Methoxy-phenyl)-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 279: *N*-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-*N'*-phenyl-benzene-1,4-diamine,

Compound 280: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-morpholin-4-yl-phenyl)-amine,

Compound 281: (2-Fluoro-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 282: (1-Benzyl-piperidin-4-yl)-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 283: (4-Butyl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 284: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-phenoxy-phenyl)-amine,

Compound 285: 4-{[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-methyl}-benzenesulfonamide,

Compound 286: rac-1-Dimethylamino-3-{4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-phenoxy}-3-propan-2-ol,

Compound 287: *N*-[6-(4-Methoxy-phenyl)-5-methyl-pyrimidin-4-yl]-benzene-1,4-amine,

Compound 288: *N*-[6-(3-Amino-phenyl)-5-methyl-pyrimidin-4-yl]-benzene-1,4-amine,

Compound 289: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-piperidin-4-yl-amine,

Compound 290: 4-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester,

Compound 291: Cyclohexyl-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 292: 4-{6-[2-(2-Morpholin-4-yl-ethoxy)-phenyl]-pyrimidin-4-ylamino}-benzoic acid methyl ester,

Compound 293: 2-Methoxy-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzoic acid methyl ester,

Compound 294: {4-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-acetic acid,

Compound 295: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(3-nitro-phenyl)-amine,

Compound 296: {3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-methanol,

Compound 297: [6-(2-Benzyloxy-phenyl)-pyrimidin-4-yl]-phenyl-amine,

Compound 298: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-phenyl-amine,
Compound 299: (4-Fluorophenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,
Compound 300: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(3-phenoxy-phenyl)-amine,
Compound 301: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(3-methylsulfanyl-phenyl)-amine,
Compound 302: [6-(2-Benzyloxy-phenyl)-pyrimidin-4-yl]-piperidin-4-yl-amine,
Compound 303: 3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenol,
Compound 304: 1-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-ethanone,
Compound 305: 2-Chloro-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzoic acid,
Compound 306: {4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-butyl}-carbamic acid tert-butyl ester,
Compound 307: [6-(2-Benzyloxy-phenyl)-pyrimidin-4-yl]-(1-methanesulfonyl-2,3-dihydro-1*H*-indol-6-yl)-amine,
Compound 308: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-piperidine-1-carboxylic acid tert-butyl ester,
Compound 309: 4-[6-(2-Amino-phenyl)-pyrimidin-4-ylamino]-benzoic acid methyl ester,
Compound 310: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-methylsulfanyl-phenyl)-amine,
Compound 311: N^1-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-butane-1,4-diamine,
Compound 312: 1-{4-[6-(2-Benzyloxy-phenyl)-pyrimidin-4-ylamino]-phenoxy}-3-dimethylamino-propan-2-ol,
Compound 313: (1-Methanesulfonyl-2,3-dihydro-1*H*-indol-6-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,
Compound 314: *N*-(2-Amino-cyclohexyl)-4-[6-(benzotriazol-1-yloxy)-pyrimidin-4-ylamino]-benzamide,
Compound 315: (2-{4-[6-(Benzotriazol-1-yloxy)-pyrimidin-4-ylamino]-benzoylamino}-cyclohexyl)-carbamic acid tert-butyl ester,
Compound 316: 1-{3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-ethanone,
Compound 317: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-piperidin-1-yl-phenyl)-amine,

Compound 318: 3-Hydroxy-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzoic acid methyl ester,

Compound 319: 2-Hydroxy-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzoic acid methyl ester,

Compound 320: 4-Amino-butane-1-sulfonic acid {5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-amide,

Compound 321: (3-{6-[3-(4-Amino-butane-1-sulfonylamino)-4-methyl-phenylamino]-pyrimidin-4-yl}-phenyl)-carbamic acid *9H*-fluoren-9-ylmethyl ester,

Compound 322: 3-Methoxy-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzoic acid methyl ester,

Compound 323: 4-{6-[2-(2-Piperidin-1-yl-ethoxy)-phenyl]-pyrimidin-4-ylamino}-benzoic acid methyl ester,

Compound 324: 4-{-6-[2-(2-Dimethylamino-ethoxy)-phenyl]-pyrimidin-4-ylamino}-benzoic acid methyl ester,

Compound 325: 4-{-6-[2-(2-Diisopropylamino-ethoxy)-phenyl]-pyrimidin-4-ylamino}-benzoic acid methyl ester,

Compound 326: 4-{-6-[2-(2-Diethylamino-ethoxy)-phenyl]-pyrimidin-4-ylamino}-benzoic acid methyl ester,

Compound 327: (S,S)-4-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzoylamino}-pyrrolidine-2-carboxylic acid methyl ester,

Compound 328: (S,S)-4-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzoylamino}-pyrrolidine-2-carboxylic acid,

Compound 329: (S,S)-6-[(4-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzoylamino}-pyrrolidine-2-carbonyl)-amino]-hexanoic acid,

Compound 330: *N*-Cyclopentyl-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzamide,

Compound 331: 3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 332: (3-Methanesulfonyl-phenyl)-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 333: 2-{3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfoyl}-ethanol,

Compound 334: *N*-(4,6-Dimethyl-pyrimidin-2-yl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 335: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-*N*-thiazol-2-yl-benzenesulfonamide,

Compound 336: (1-Benzyl-piperidin-3-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 337: 3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-azepan-2-one,

Compound 338: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-*N*-phenyl-benzenesulfonamide,

Compound 339: rac-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(1,2,3,4-tetrahydro-naphthalen-1-yl)-amine,

Compound 340: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(2,2,6,6-tetramethyl-piperidin-4-yl)-amine,

Compound 341: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-*N*-methyl-benzenesulfonamide,

Compound 342: (1,1-Dioxo-1*H*-1λ^6–benzo[*b*]thiophen-6-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 343: *N*-Acetyl-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 344: *N*-(2,6-Dimethyl-pyrimidin-4-yl)-4-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 345: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[4-(piperidine-1-sulfonyl)-phenyl]-amine,

Compound 346: 3-{3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenoxy}-piperidine-1-carboxylic acid tert-butyl ester,

Compound 347: [6-(2-Fluoro-6-methoxy-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine,

Compound 348: [6-(4-Fluoro-2-methoxy-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine,

Compound 349: [6-(5-Fluoro-2-methoxy-phenyl)-pyrimidin-4-yl]-(3-methanesulfonyl-phenyl)-amine,

Compound 350: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-pyridin-3-yl-amine,

Compound 351: 2-{4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-phenyl}-ethanol,

Compound 352: (9,9-Dioxo-9,10-dihydro-9λ^6–thia-10-aza-phenanthren-3-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 353: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(1-methyl-1*H*-indazol-6-yl)-amine,

Compound 354: Benzo[1,2,5]thiadiazol-4-yl-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 355: Benzo[1,2,5]thiadiazol-5-yl-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 356: rac-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-[3-(piperidin-3-yloxy)-phenyl]-amine,

Compound 357: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-{1-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-1*H*-indazol-5-yl}-amine,

Compound 358: (1*H*-Indol-5-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 359: (3-Methanesulfinyl-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 360: (1*H*-Indazol-5-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 361: 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-thiophene-3-carboxylic acid methyl ester,

Compound 362: 4-Methanesulfonyl-benzyl-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 363: (5-Chloro-1*H*-indazol-3-yl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine,

Compound 364: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(5-methyl-isoxazol-3-yl)-amine,

Compound 365: 3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-*N,N*-dimethyl-benzenesulfonamide,

Compound 366: *N*-Ethyl-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 367: 3-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-*N*-propyl-benzenesulfonamide,

Compound 368: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(2-methyl-1*H*-indol-5-yl)-amine,

Compound 369: *N*-(2-Methoxy-ethyl)-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 370: *N*-tert-Butyl-3-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-benzenesulfonamide,

Compound 371: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-pyridin-2-ylmethyl-amine,

Compound 372: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-pyridin-3-ylmethyl-amine,

Compound 373: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-pyridin-4-ylmethyl-amine,

Compound 374: 5-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-benzenesulfonamide,

Compound 375: *N*-(2-Methoxy-ethyl)-5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-benzenesulfonamide,

Compound 376: *N*-(2-Hydroxy-ethyl)-5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-benzenesulfonamide,

Compound 377: N,N-Diethyl-N'-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-benzene-1,4-diamine,

Compound 378: 1-(4-Chloro-3-trifluoromethyl-phenyl)-3-{5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-urea,

Compound 379: 1-Cyclohexyl-3-{5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-urea,

Compound 380: [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-(4-pyrrolidin-1-yl-phenyl)-amine,

Compound 381: 4-Chloro-N-1-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-benzene-1,3-diamine,

Compound 382: 1-Isopropyl-3-{5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-urea,

Compound 383: 1-{5-[6-(2-Methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-3-(2-morpholin-4-yl-ethyl)-urea,

Compound 384: 1-(2-Dimethylamino-ethyl)-3-{5-[6-(2-methoxy-phenyl)-pyrimidin-4-ylamino]-2-methyl-phenyl}-urea,

Compound 385: (4-Chloro-3-nitro-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine.

34. A compound according to one of claims 1 to 33 for use as pharmaceutically active agent.

35. Use of at least one compound according to one of claims 1 to 34 for the preparation of a pharmaceutical composition for the prophylaxis and / or treatment of infectious diseases, including opportunistic diseases, prion diseases, immunological diseases, autoimmune diseases, bipolar and clinical disorders, cardiovascular diseases, cell proliferative diseases, diabetes, inflammation, transplant rejections, erectile dysfunction, neurodegenerative diseases and stroke.

36. Use according to claim 35, wherein the infectious diseases, including opportunistic diseases, are virally induced infectious diseases, including opportunistic diseases.

37. Use according to claim 36, wherein the virally induced infectious diseases, including opportunistic diseases, are caused by retroviruses, human endogenous retroviruses, lentiviruses, oncoretroviruses, hepadnaviruses, herpesviruses, flaviviridae, and/or adenoviruses.

38. Use according to claim 37, wherein the lentivirus, oncoretrovirus, hepadnavirus or herpesivirus is selected from the group comprising: HIV-1, HIV-2, FIV, BIV, SIVs, SHIVs, CAEV, VMV or EIAV, preferably HIV-1 and HIV-2; HTLV-I, HTLV-II or BLV, preferably HTLV-I or HTLV-II; HBV, GSHV or WHV, preferably HBV; HSV I, HSV II, EBV, VZV, HCMV or HHV 8, preferably HCMV.

39. Use according to claim 35 or 36, wherein the infective disease including opportunistic infection is selected from the group comprising AIDS, Alveolar Hydatid Disease (AHD, Echinococcosis), Amebiasis (Entamoeba histolytica Infection), Angiostrongylus Infection, Anisakiasis, Anthrax, Babesiosis (Babesia Infection), Balantidium Infection (Balantidiasis), Baylisascaris Infection (Raccoon Roundworm), Bilharzia (Schistosomiasis), Blastocystis hominis Infection (Blastomycosis), Boreliosis, Botulism, Brainerd Diarrhea, Brucellosis, BSE (Bovine Spongiform Encephalopathy), Candidiasis, Capillariasis (Capillaria Infection), CFS (Chronic Fatigue Syndrome), Chagas Disease (American Trypanosomiasis), Chickenpox (Varicella-Zoster virus), Chlamydia pneumoniae Infection, Cholera, Chronic Fatigue Syndrome, CJD (Creutzfeldt-Jakob Disease), Clonorchiasis (Clonorchis Infection), CLM (Cutaneous Larva Migrans, Hookworm Infection), Coccidioidomycosis, Conjunctivitis, Coxsackievirus A16 (Hand, Foot and Mouth Disease), Cryptococcosis, Cryptosporidium Infection (Cryptosporidiosis), Culex mosquito (Vector of West Nile Virus), Cutaneous Larva Migrans (CLM), Cyclosporiasis (Cyclospora Infection), Cysticercosis (Neurocysticercosis), Cytomegalovirus Infection, Dengue / Dengue Fever, Dipylidium Infection (Dog and Cat Flea Tapeworm), Ebola Virus Hemorrhagic Fever, Echinococcosis (Alveolar Hydatid Disease), Encephalitis, Entomoeba coli Infection, Entomoeba dispar Infection, Entomoeba hartmanni Infection, Entomoeba histolytica Infection

(Amebiasis), Entomoeba polecki Infection, Enterobiasis (Pinworm Infection), Enterovirus Infection (Non-Polio), Epstein-Barr Virus Infection, Escherichia coli Infection, Foodborne Infection, Foot and mouth Disease, Fungal Dermatitis, Gastroenteritis, Group A streptococcal Disease, Group B streptococcal Disease, Hansen's Disease (Leprosy), Hantavirus Pulmonary Syndrome, Head Lice Infestation (Pediculosis), Helicobacter pylori Infection, Hematologic Disease, Hendra Virus Infection, Hepatitis (HCV, HBV), Herpes Zoster (Shingles), HIV Infection, Human Ehrlichiosis, Human Parainfluenza Virus Infection, Influenza, Isosporiasis (Isospora Infection), Lassa Fever, Leishmaniasis, Kala-azar (Kala-azar, Leishmania Infection), Leprosy, Lice (Body lice, Head lice, Pubic lice), Lyme Disease, Malaria, Marburg Hemorrhagic Fever, Measles, Meningitis, Mosquito-borne Diseases, Mycobacterium avium Complex (MAC) Infection, Naegleria Infection, Nosocomial Infections, Nonpathogenic Intestinal Amebae Infection, Onchocerciasis (River Blindness), Opisthorciasis (Opisthorcis Infection), Parvovirus Infection, Plague, PCP (Pneumocystis carinii Pneumonia), Polio; Q Fever, Rabies, Respiratory Syncytial Virus (RSV) Infection, Rheumatic Fever, Rift Valley Fever, River Blindness (Onchocerciasis), Rotavirus Infection, Roundworms Infection, Salmonellosis, Salmonella Enteritidis, Scabies, Shigellosis, Shingles, Sleeping Sickness, Smallpox, Streptococcal Infection, Tapeworm Infection (Taenia Infection), Tetanus, Toxic Shock Syndrome, Tuberculosis, Ulcers (Peptic Ulcer Disease), Valley Fever; Vibrio parahaemolyticus Infection, Vibrio vulnificus Infection, Viral Hemorrhagic Fever, Warts, Waterborne infectious Diseases, West Nile Virus Infection (West Nile Encephalitis), Whooping Cough, Yellow Fever, tuberculosis, leprosy, mycobacteria-induced meningitis.

40. Use according to claim 35, wherein the prion diseases is selected from the group comprising Scrapie, TME, CWD, BSE, CJD, vCJD, GSS, FFI, Kuru, and Alpers Syndrome.

41. Use according to claim 35, wherein the immunological disease and/or autoimmune disease is selected from the group comprising:
asthma, diabetes, rheumatic diseases, AIDS, rejection of transplanted organs and tissues, rhinitis, chronic obstructive pulmonary diseases, osteoporisis, ulcerative colitis, sinusitis, lupus erythematosus, recurrent infections, atopic dermatitis / eczema and occupational allergies, food

allergies, drug allergies, severe anaphylactic reactions, anaphylaxis, manifestations of allergic diseases, primary immunodeficiencies, antibody deficiency states, cell mediated immunodeficiencies, severe combined immunodeficiency, DiGeorge syndrome, Hyper-IgE syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia, immune mediated cancers, white cell defects, autoimmune diseases, systemic lupus erythematosus, rheumatoid arthritis (RA), multiple sclerosis (MS), immune-mediated or Type 1 Diabetes Mellitus, immune mediated glomerulonephritis, scleroderma, pernicious anemia, alopecia, pemphigus, pemphigus vulgaris, myasthenia gravis, inflammatory bowel diseases, Crohn's disease, psoriasis, autoimmune thyroid diseases, Hashimoto's disease, dermatomyositis, goodpastture syndrome, myasthenia gravis pseudoparalytica, ophtalmia sympatica, phakogene uveitis, chronical agressivce hepatitis, primary billiary cirrhosis, autoimunehemolytic anemy, Werlof disease.

42. Use according to claim 35, wherein the bipolar and/or clinical disorder is selected from the group comprising: adjustment disorders, anxiety disorders, delirium, dementia, amnestic and other cognitive disorders, disorders usually first diagnosed in infancy, childhood, or adolescence, dissociative disorders, eating disorders, factitious disorders, impulse-control disorders, mental disorders due to a general medical condition, mood disorders, other conditions that may be a focus of clinical attention, personality disorders, schizophrenia and other psychotic disorders, sexual and gender identity disorders, sleep disorders, somatoform disorders, substance-related disorders, generalized anxiety disorder, panic disorder, phobia, agoraphobia, obsessive-compulsive disorder, stress, acute stress disorder, anxiety neurosis, nervousness, phobia, posttraumatic stress disorder, posttraumatic stress disorder (PTSD), abuse, ADHD, obsessive-compulsive disorder (OCD), manic depressive psychosis, specific phobias, social phobia, adjustment disorder with anxious features.

43. Use according to claim 42, wherein the anxiety disorders, delirium, dementia, amnestic and other cognitive disorders, disorders usually first diagnosed in infancy, childhood, or adolescence, dissociative disorders, eating disorders, mood disorders, schizophrenia and other psychotic disorders, sexual and gender identity disorders, sleep disorders, somatoform disorders, substance-related disorders are selected from the

group comprising: acute stress disorder, agoraphobia without history of panic disorder, anxiety disorder due to general medical condition, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, specific phobia, social phobia, substance-induced anxiety disorder, delirium due to a general medical condition, substance intoxication delirium, substance withdrawal delirium, delirium due to multiple etiologies, Alzheimer's, Creutzfeldt-Jakob disease, head trauma, Huntington's disease, HIV disease, Parkinson's disease, Pick's disease, substance-induced persisting, vascular, dementia due to other general medical conditions, dementia due to multiple etiologies, amnestic disorder due to a general medical condition, substance-induced persisting amnestic disorder, mental retardation, learning disorders, mathematics disorder, reading disorder, disorder of written expression, learning disorder, motor skills disorders, developmental coordination disorder, communication disorders, expressive language disorder, phonological disorder, mixed receptive-expressive language disorder, stuttering, pervasive developmental disorders, Asperger's disorder, autistic disorder, childhood disintegrative disorder, Rett's disorder, pervasive developmental disorder, attention-deficit/hyperactivity disorder (ADHD), conduct disorder, oppositional defiant disorder, feeding disorder of infancy or early childhood, pica, rumination disorder, tic disorders, chronic motor or vocal tic disorder, Tourette's disorder, elimination disorders, encopresis, enuresis, selective mutism, separation anxiety disorder, reactive attachment disorder of infancy or early childhood, stereotypic movement disorder, dissociative amnesia, depersonalization disorder, dissociative fugue, dissociative identity disorder, anorexia nervosa, bulimia nervosa, mood episodes, major depressive episode, hypomanic episode, manic episode, mixed episode, depressive disorders, dysthymic disorder, major depressive disorder, single episode, recurrent, bipolar disorders, bipolar I disorder, bipolar II disorder, cyclothymic disorder, mood disorder due to a general medical condition, substance-induced mood disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, delusions, hallucinations, substance-induced psychotic disorder, female sexual arousal disorder, orgasmic disorders, premature ejaculation, sexual pain disorders, dyspareunia, vaginismus, sexual dysfunction due to a general medical condition, female dyspareunia, female hypoactive sexual

desire disorder, male erectile disorder, male hypoactive sexual desire disorder, male dyspareunia, other female sexual dysfunction, other male sexual dysfunction, substance-induced sexual dysfunction, sexual dysfunction, paraphilias, exhibitionism, fetishism, frotteurism, pedophilia, masochism, sadism, transvestic fetishism, voyeurism, paraphilia, gender identity disorder, dyssomnias, breathing-related sleep disorder, circadian rhythm sleep disorder, hypersomnia, hypersomnia related to another mental disorder, insomnia, insomnia related to another mental disorder, narcolepsy, dyssomnia, parasomnias, nightmare disorder, sleep terror disorder, sleepwalking disorder, parasomnia, body dysmorphic disorder, conversion disorder, hypochondriasis, pain disorder, somatization disorder, undifferentiated somatoform disorder, alcohol related disorders, amphetamine related disorders, caffeine related disorders, cannabis related disorders, cocaine related disorders, hallucinogen related disorders, inhalant related disorders, nicotine related disorders, opioid related disorders, psychotic disorder, psychotic disorder, phencyclidine-related disorder, abuse, persisting amnestic disorder, anxiety disorder, persisting dementia, dependence, intoxication, intoxication delirium, mood disorder, psychotic disorder, withdrawal, withdrawal delirium, sexual dysfunction, sleep disorder.

44. Use according to claim 35, wherein the cardiovascular diseases are selected from the group consisting of:
adult congenital heart disease, aneurysm, stable angina, unstable angina, angina pectoris, angioneurotic edema, aortic valve stenosis, aortic aneurysm, arrhythmia, arrhythmogenic right ventricular dysplasia, arteriosclerosis, arteriovenous malformations, atrial fibrillation, Behcet syndrome, bradycardia, cardiac tamponade, cardiomegaly, congestive cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, cardiovascular disease prevention, carotid stenosis, cerebral hemorrhage, Churg-Strauss syndrome, diabetes, Ebstein's Anomaly, Eisenmenger complex, cholesterol embolism, bacterial endocarditis, fibromuscular dysplasia, congenital heart defects, heart diseases, congestive heart failure, heart valve diseases, heart attack, epidural hematoma, hematoma, subdural, Hippel-Lindau disease, hyperemia, hypertension, pulmonary hypertension, hypertrophic growth, left ventricular hypertrophy, right ventricular hypertrophy, hypoplastic left heart syndrome, hypotension, intermittent claudication, ischemic heart disease, Klippel-Trenaunay-Weber

syndrome, lateral medullary syndrome, long QT syndrome mitral valve prolapse, moyamoya disease, mucocutaneous lymph node syndrome, myocardial infarction, myocardial ischemia, myocarditis, pericarditis, peripheral vascular diseases, phlebitis, polyarteritis nodosa, pulmonary atresia, Raynaud disease, restenosis, Sneddon syndrome, stenosis, superior vena cava syndrome, syndrome X, tachycardia, Takayasu's arteritis, hereditary hemorrhagic telangiectasia, telangiectasis, temporal arteritis, tetralogy of fallot, thromboangiitis obliterans, thrombosis, thromboembolism, tricuspid atresia, varicose veins, vascular diseases, vasculitis, vasospasm, ventricular fibrillation, Williams syndrome, peripheral vascular disease, varicose veins and leg ulcers, deep vein thrombosis, Wolff-Parkinson-White syndrome.

45. Use according to claim 35, wherein the proliferative disease is selected from the group comprising:
adenocarcinoma, choroidal melanoma, acute leukemia, acoustic neurinoma, ampullary carcinoma, anal carcinoma, astrocytoma, basal cell carcinoma, pancreatic cancer, desmoid tumor, bladder cancer, bronchial carcinoma, breast cancer, Burkitt's lymphoma, corpus cancer, CUP-syndrome (carcinoma of unknown primary), colorectal cancer, small intestine cancer, small intestinal tumors, ovarian cancer, endometrial carcinoma, ependymoma, epithelial cancer types, Ewing's tumors, gastrointestinal tumors, gastric cancer, gallbladder cancer, gall bladder carcinomas, uterine cancer, cervical cancer, cervix, glioblastomas, gynecologic tumors, ear, nose and throat tumors, hematologic neoplasias, hairy cell leukemia, urethral cancer, skin cancer, skin testis cancer, brain tumors (gliomas), brain metastases, testicle cancer, hypophysis tumor, carcinoids, Kaposi's sarcoma, laryngeal cancer, germ cell tumor, bone cancer, colorectal carcinoma, head and neck tumors (tumors of the ear, nose and throat area), colon carcinoma, craniopharyngiomas, oral cancer (cancer in the mouth area and on lips), cancer of the central nervous system, liver cancer, liver metastases, leukemia, eyelid tumor, lung cancer, lymph node cancer (Hodgkin's/Non-Hodgkin's), lymphomas, stomach cancer, malignant melanoma, malignant neoplasia, malignant tumors gastrointestinal tract, breast carcinoma, rectal cancer, medulloblastomas, melanoma, meningiomas, Hodgkin's disease, mycosis fungoides, nasal cancer, neurinoma, neuroblastoma, kidney cancer, renal cell carcinomas, non-Hodgkin's lymphomas, oligodendroglioma, esophageal carcinoma,

osteolytic carcinomas and osteoplastic carcinomas, osteosarcomas, ovarial carcinoma, pancreatic carcinoma, penile cancer, plasmocytoma, prostate cancer, pharyngeal cancer, rectal carcinoma, retinoblastoma, vaginal cancer, thyroid carcinoma, Schneeberger disease, esophageal cancer, spinalioms, T-cell lymphoma (mycosis fungoides), thymoma, tube carcinoma, eye tumors, urethral cancer, urologic tumors, urothelial carcinoma, vulva cancer, wart appearance, soft tissue tumors, soft tissue sarcoma, Wilm's tumor, cervical carcinoma and tongue cancer.

46. Use according to claim 35, wherein said diabetes is selected from Type I diabetes or Type II diabetes.

47. Use according to claim 35, wherein said inflammation is mediated by the cytokines TNF-α, IL-1ß, GM-CSF, IL-6 and/or IL-8.

48. Use according to claim 35 or 47 wherein the inflammatory disease is caused, induced, initiated and/or enhanced by bacteria, viruses, prions, parasites, fungi, and/or caused by irritative, traumatic, metabolic, allergic, autoimmune, or idiopathic reasons.

49. Use according to claim 48 wherein the viruses and bacteria are selected from the group comprising human immunodeficiency virus-I, herpes viruses, herpes simplex virus, herpes zoster virus, cytomegalovirus, mycoplasma pulmonis, ureaplasma urealyticum, mycoplasma pneumoniae, chlamydia pneumoniae, C. pneumoniae, Helicobacter pylori, and propriono-bacterium.

50. Use according to any one of the claims 35, 47 – 49, wherein the inflammatory disease is selected from the group comprising inflammatory diseases of the central nervous system (CNS), inflammatory rheumatic diseases, inflammatory diseases of blood vessels, inflammatory diseases of the middle ear, inflammatory bowel diseases, inflammatory diseases of the skin, inflammatory disease uveitis, inflammatory diseases of the larynx.

51. Use according to claim 50 wherein the inflammatory diseases of the central nervous system (CNS), inflammatory rheumatic diseases, inflammatory diseases of blood vessels, inflammatory diseases of the middle ear, inflammatory bowel diseases, inflammatory diseases of the skin,

inflammatory disease uveitis, inflammatory diseases of the larynx are selected from the group comprising:

abscessation, acanthameba, acanthamebiasis, acne vulgaris, actinomycosis, acute inflammatory dermatoses, acute laryngeal infections of adults, acute multifocal placoid pigmentary epitheliopathy, acute (thermal) injury, acute retinal necrosis, acute suppurative otitis media, algal disorders, allergic contact dermatitis, amyloidosis angioedema, ankylosing spondylitis, aspergillosis, atopic dermatitis, Aujeszky's disease, autoantibodies in vasculitis, babesiosis, bacterial disorders, bacterial laryngitis, bacterial meningitis, Behcet's disease, birdshot choroidopathy, blastomycosis, borna disease, brucellosis, bullous myringitis, bursitis, candidiasis, canine distemper encephalomyelitis, canine distemper encephalomyelitis in immature animals, canine ehrlichiosis, canine herpes virus encephalomyelitis, cholesteatoma, chronic (granulomatous) diseases, chronic inflammatory dermatoses, chronic relapsing encephalomyelitis, chronic suppurative otitis media, cicatricial pemphigoid, coccidiomycosis, coccidioidomycosis, common upper respiratory infection, contact ulcer and granuloma, Crohn's disease, cryptococcosis, cysticercosis, dermatomyositis, diphtheria, discoid lupus erythematosus, drug-induced vasculitis, drug or hypersensitivity reaction, encephalitozoonosis, eosinophilic meningoencephalitis, erythemal multiforme (EM minor), feline leukemia virus, feline immunodeficiency virus, feline infectious peritonitis, feline polioencephalomyelitis, feline spongiform encephalopathy, fibromyositis, Fuch's heterochromic cyclitis, gastroesophageal (laryngopharyngeal) reflux disease, giant cell arteritis, glanders, glaucomatocyclitic crisis, gonorrhea granular myringitis, granulomatous meningoencephalomyelitis, herpes simplex, histoplasmosis, idiopathic diseases, idiopathic inflammatory disorders, immune and idiopathic disorders, infections of the immunocompromised host, infectious canine hepatitis, inhalation laryngitis, interstitial nephritis, irritant contact dermatitis, juvenile rheumatoid arthritis, Kawasaki's disease, La Crosse virus encephalitis, laryngeal abscess, laryngotracheitis (croup), leishmaniasis, lens-induced uveitis, leprosy, leptospirosis, leukemia, lichen planus, lupus, lyme disease, lymphoma, meningitis, meningoencephalitis in greyhounds, miscellaneous meningitis / meningoencephalitis, microscopic polyangiitis, multifocal choroiditis, multifocal distemper encephalomyelitis in mature animals, multiple sclerosis, muscle tension dysphonias, mycotic (fungal) diseases, mycotic

diseases of the CNS, necrotizing encephalitis, neosporosis, old dog encephalitis, onchocerciasis, parasitic encephalomyelitis, parasitic infections, pars planitis, parvovirus encephalitis, pediatric laryngitis, pollution and inhalant allergy, polymyositis, post-vaccinal canine distemper encephalitis, post-vaccinal rabies, prion protein induced diseases, protothecosis, protozoal encephalitis-encephalomyelitis, psoriasis, psoriatic arthritis, pug dog encephalitis, pyogranulomatous meningoencephalomyelitis, rabies, radiation injury, radiation laryngitis, radionecrosis, relapsing polychondritis, Reiters's syndrome, retinitis pigmentosa, retinoblastoma, rheumatoid arthritis, rickettsial disorders, rocky mountain spotted fever, salmon poisoning, sarcocystosis, sarcoidosis, schistosomiasis, scleroderma, scleroma, serpiginous choroiditis, shaker dog disease, Sjogren's syndrome, spasmodic croup, spirochetal (syphilis) diseases, spongiotic dermatitis, sporotrichosis, steroid responsive meningitis-arteritis, Stevens-Johnson syndrome (SJS, EM major), supraglottitis (epiglottitis), sympathetic ophthalmia, syngamus laryngeus, syphilis, systemic lupus erythematosus, systemic vasculitis in sarcoidosis, Takayasu's arteritis, tendinitis (tendonitis), thromboangiitis obliterans (Buerger's Disease), tick-borne encephalitis in dogs, toxic epidermal necrolysis (TEN), toxocariasis, toxoplasmosis, trauma, traumatic laryngitis, trichinosis, trypanosomiasis, tuberculosis, tularemia, ulcerative colitis, urticaria (hives), vasculitis, vasculitis and malignancy, vasculitis and rheumatoid arthritis, vasculitis in systemic lupus erythematosus, vasculitis in the idiopathic inflammatory myopathies, vasculitis of the central nervous system, vasculitis secondary to bacterial, fungal, and parasitic infection, viral disorders, viral laryngitis, vitiligo, vocal abuse, vocal-cord hemorrhage, Vogt Koyanagi Harada syndrome, Wegener's granulomatosis, and Whipple's disease.

52. Use according to claim 35, wherein the transplant rejection is selected from the group comprising heart transplant rejection, heart-lung transplant rejection, lung transplant rejection, liver transplant rejection, kidney transplant rejection, pancreas transplant rejection, spleen transplant rejection, skin transplant rejection, tissue transplant rejection, bone marrow transplant rejection, spinal marrow transplant rejection, hormone producing glands transplant rejection, gonads and gonadal gland transplant rejection, graft-versus-host-diseases and host-versus-graft-diseases.

53. Use according to claim 35, wherein the neurodegenerative diseases are selected from the group comprising:
Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, AIDS-related dementia, retinitis pigmentosa, spinal muscular atrophy and cerebrellar degeneration, fragile X-associated tremor/ataxia syndrome (FXTAS), progressive supranuclear palsy (PSP), and striatonigral degeneration (SND), which is included with olivopontocerebellear degeneration (OPCD), and Shy Drager syndrome (SDS) in a syndrome known as multiple system atrophy (MSA).

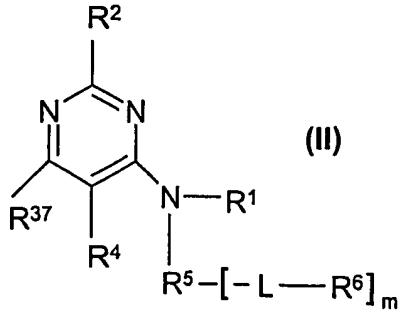
54. Use of a compound according to any one of claims 1 to 34 as an inhibitor for a protein kinase, preferably a cellular protein kinase.

55. Use according to claim 54, wherein said cellular protein kinase is selected from the group compring: Cyclin-dependent protein kinase (CDK), protein kinase C, c-Raf, Akt, CKI, IKKβ, MAP kinases/ERKs, MAP kinases/JNKs, EGF receptor, InsR, PDGF receptor, c-Met, p70S6K, ROCK, Rsk1, Src, Abl, p56Lck, c-kit, CaMk2β, CaMk2δ, CaMk2γ, CSK or GSK-3α and ß, MLK, MRK-alpha, yes, CSK, human cdc2-like protein kinase (similar to CDC2L5), Crk7, MAK and growth factor receptor similar to fibroblast growth factor receptor 3 (FGFR-3).

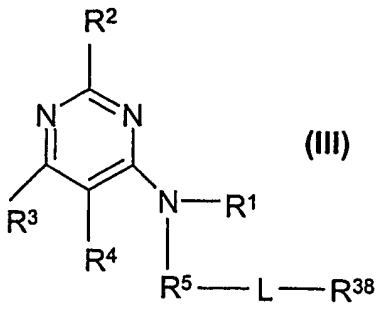
56. Use according to claim 55, wherein said cyclin-dependent protein kinase is selected from the group comprising:
CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, CDK11, CrkRS (Crk7, CDC2-related protein kinase 7), CDKL1 (cyclin-dependent kinase-like 1); KKIALRE, CDKL2 (cyclin-dependent kinase-like 2), KKIAMRE, CDKL3 (cyclin-dependent kinase-like 3), NKIAMRE, CDKL4, similar to cyclin-dependent kinase-like 1, CDC2L1 (cell division cycle 2-like 1), PITSLRE B, CDC2L1 (cell division cycle 2-like 1), PITSLRE A, CDC2L5 (cell division cycle 2-like 5), PCTK1 (PCTAIRE protein kinase 1), PCTK2 (PCTAIRE protein kinase 2), PCTK3 (PCTAIRE protein kinase 3) or PFTK1 (PFTAIRE protein kinase 1).

57. Pharmaceutical composition comprising at least one compound according to any one of claims 1 to 32 as an active ingredient, together with at least one pharmaceutically acceptable carrier, excipient and/or diluent.

58. A medium for separating at least one nucleotide binding protein from a pool of proteins, the medium comprising at least one compound of the general formula (II) and/or formula (III)



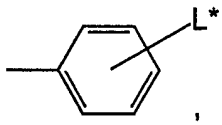
(II)



(III)

wherein

R^1, R^2, R^3, R^4, R^5, R^6, **L** and **m** have the meanings as defined in claim 1,

R^{37} and R^{38} are independently of each other selected from  ,

–L*, substituted or unsubstituted C_1–C_6 alkyl–L*, substituted or unsubstituted C_3–C_8 cycloalkyl–L*, substituted or unsubstituted heterocyclyl–L*, substituted or unsubstituted aryl–L*, or substituted or unsubstituted heteroaryl–L*;

L* is selected from $-X^1-H$, $-X^3$, $-X^1-X^3$;

X^1 and X^2 are independently of each other selected from –NH–, –S–, –O–, –N(C_1–C_6 alkyl)–, –COO–, –O–CO–, –CO–NH–, –NH–CO–, –O–CO–NH–, –NH–CO–O–, –NH–CO–NH–, –O–CO–O–, –NH–C(NH)–NH–, $-NH-SO_2-$, $-SO_2-NH-$;

X^1–H and Y^1–H are independently of each other selected from $-NH_2$, –SH, –OH, –N(C_1–C_6 alkyl)H, –COOH, $-CO-NH_2$, $-O-CO-NH_2$, $-NH-SO_2H$, $-NH-SO_3H$, $-SO_2-NH_2$, $-NH-C(NH)-NH_2$,

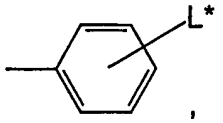
X^3 is selected from $-(CH_2)_a-X^4$, $-(CH_2)_a-CO-X^4$, $-(CH_2)_a-NH-SO_2-X^4$, $-(CH_2)_a-Y^1-H$, $-(CH_2)_a-X^2-(CH_2)_b-X^4$, $-(CH_2)_a-X^2-(CH_2)_b-Y^1-H$;

X^4 is selected from –Cl, –Br, –I, $-N_3$, $-OOC-C_1$-C_6 alkyl, $-O-SO_2-CH_3$, $-O-SO_2-p-C_6H_4-CH_3$;

a and **b** are independently of each other integer from 1 – 10;

immobilized on a support material.

59. The medium according to claim 58, wherein R^1, R^2 and R^4 are independently of each other selected from –H or linear or branched C_1–C_4 alkyl;
R^3 represents substituted or unsubstituted phenyl, preferably substituted phenyl, wherein the phenyl is partially or fully substituted with members of the group consisting of: linear or branched C_1–C_4 alkoxy, $-OCH_2$–Phenyl, or $-NH_2$, and wherein phenyl is preferably monosubstituted;
R^5 represents substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, wherein phenyl is preferably substituted with linear or branched C_1–C_4 alkyl,
L is selected from the group comprising:
–NH–CO–, $-NH-SO_2-$, $-SO_2-NH-$, –CO–NH–, –NH–CO–NH–, –NH–CO–O–, –NH–CS–NH–, –NH–C(NH)–NH–, –CO–, –CO–O–, –SO–, $-SO_2-$, $-SO_3-$
and
m is selected to be 1 and
R^6 is selected from the group comprising: –H, linear or branched C_1–C_4 alkyl, monosubstituted phenyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroaryl or substituted or unsubstituted C_3–C_8 cycloalkyl, and

R^{37} is selected to be 

,

or wherein
R^{38} is selected from substituted or unsubstituted C_3–C_8 cycloalkyl–L*, substituted or unsubstituted aryl–L*, substituted or unsubstituted C_1–C_6 alkyl–L*, substituted or unsubstituted heterocyclyl–L*, wherein the heterocyclyl is selected from pyrrolidinyl or piperidinyl..

60. The medium according to claims 58 or 59, wherein
X^1 is selected to be –NH– or –O–,

Y^1–**H** is selected to be $-NH_2$ or $-N(C_1-C_6$ alkyl)H and preferably $-NH_2$,
a and **b** are independently of each other selected to be an integer from 1 to 6, preferably from 2 to 4.

61. The medium according to claim 60, wherein at least one of the compounds 1 – 205, preferably compound 102 or 103 is immobilized on a support material.

62. The medium according to any one of claims 58 to 61, wherein the compound is covalently bound through the group Y^1 to the support material.

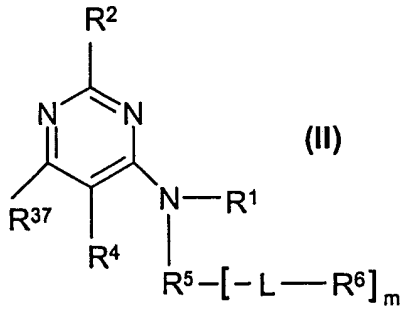
63. The medium according to claim 62, wherein the support material comprises sepharose and modified sepharose.

64. The medium according to any one of claims 58 to 63, wherein the pool of proteins is a proteome, a cell lysate or a tissue lysate.

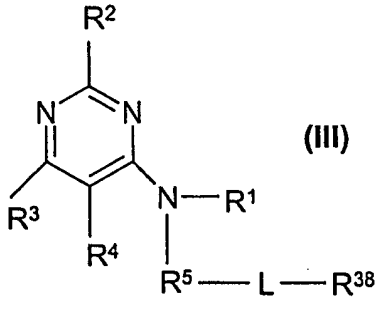
65. The medium according to any one of the claims 58 to 64, wherein the nucleotide binding protein is an ATP binding protein, preferably a kinase, more preferably a protein kinase.

66. A method for enriching, purifying or depleting at lest one nucleotide binding protein from a pool of proteins containing at least one nucleotide binding protein, the method comprising the following steps:

a) Immobilizing at least one compound of the general formula (II) and/or formula (III)

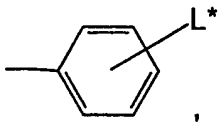


(II)



(III)

wherein
R^1, R^2, R^3, R^4, R^5, R^6, **L** and **m** have the meanings as defined in claim 1,

R^{37} and R^{38} are independently of each other selected from 

–L*, substituted or unsubstituted C_1–C_6 alkyl–L*, substituted or unsubstituted C_3–C_8 cycloalkyl–L*, substituted or unsubstituted heterocyclyl–L*, substituted or unsubstituted aryl–L*, or substituted or unsubstituted heteroaryl–L*;

L* is selected from $-X^1-H$, $-X^3$, $-X^1-X^3$;

X^1 and X^2 are independently of each other selected from –NH–, –S–, –O–, –N(C_1–C_6 alkyl)–, –COO–, –O–CO–, –CO–NH–, –NH–CO–, –O–CO–NH–, –NH–CO–O–, –NH–CO–NH–, –O–CO–O–, –NH–C(NH)–NH–, $-NH-SO_2-$, $-SO_2-NH-$;

X^1–H and Y^1–H are independently of each other selected from $-NH_2$, –SH, –OH, –N(C_1–C_6 alkyl)H, –COOH, $-CO-NH_2$, $-O-CO-NH_2$, $-NH-SO_2H$, $-NH-SO_3H$, $-SO_2-NH_2$, $-NH-C(NH)-NH_2$,

X^3 is selected from $-(CH_2)_a-X^4$, $-(CH_2)_a-CO-X^4$, $-(CH_2)_a-NH-SO_2-X^4$, $-(CH_2)_a-Y^1-H$, $-(CH_2)_a-X^2-(CH_2)_b-X^4$, $-(CH_2)_a-X^2-(CH_2)_b-Y^1-H$;

X^4 is selected from –Cl, –Br, –I, $-N_3$, –OOC–C_1-C_6 alkyl, $-O-SO_2-CH_3$, $-O-SO_2-p-C_6H_4-CH_3$;

a and b are independently of each other interger from 1 – 10;

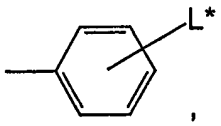
on a support material;

b) bringing the pool of proteins containing at least one nucleotide binding protein into contact with at least one compound according to the general formula (II) and/or according to the general formula (III) immobilized on the support material; and

c) separating the proteins not bound to the at least one compound according to the general formula (II) and/or according to the general formula (III) on the support material from the at least one nucleotide binding protein bound to the at least one said compound immobilized on the support material; and

d) Releasing and collecting the at least one nucleotide binding protein bound to the at least one compound according to the general formula (II) and/or according to the general formula (III) immobilized on the support material from the at least one of said compounds.

67. The method according to claim 66, wherein R^1, R^2 and R^4 are independently of each other selected from –H or linear or branched C_1–C_4 alkyl;
R^3 represents substituted or unsubstituted phenyl, preferably substituted phenyl, wherein the phenyl is partially or fully substituted with members of the group consisting of: linear or branched C_1–C_4 alkoxy, –OCH_2–Phenyl, or –NH_2, and wherein phenyl is preferably monosubstituted;
R^5 represents substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, wherein phenyl is preferably substituted with linear or branched C_1–C_4 alkyl,
L is selected from the group comprising:
–NH–CO–, –SO_2–, –NH–SO_2–, –SO_2–NH– or –CO–NH–,
and
m is selected to be 1 and
R^6 is selected from the group comprising: –H, linear or branched C_1 – C_4 alkyl, monosubstituted phenyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroaryl or substituted or unsubstituted C_3–C_8 cycloalkyl, and

R^{37} is selected to be 

,

or wherein
R^{38} is selected from substituted or unsubstituted C_3–C_8 cycloalkyl–L*, preferably unsubstituted C_3–C_8 cycloalkyl–L*, substituted or unsubstituted heterocyclyl–L*, wherein the heterocyclyl is selected from pyrrolidinyl or piperidinyl.

68. The method according to claims 66 or 67, wherein
X^1 is selected to be –NH– or –O–,
Y^1–H is selected to be –OH, –NH_2 or –N(C_1–C_6 alkyl)H, preferably –NH_2,
a and **b** are independently of each other selected to be an integer from 1 to 6, preferably from 2 to 4.

69. The method according to any one of claims 66 to 68, wherein at least one of the compounds 1 – 205, preferably compound 102 or 103 is immobilized on the support material.

70. The method according to any one of claims 66 to 69, wherein the nucleotide binding protein is an ATP binding protein, preferably a kinase, more preferably a protein kinase.

71. The method according to any one of claims 66 to 70, wherein the support material comprises sepharose and modified sepharose.

Figures

Figure 1a

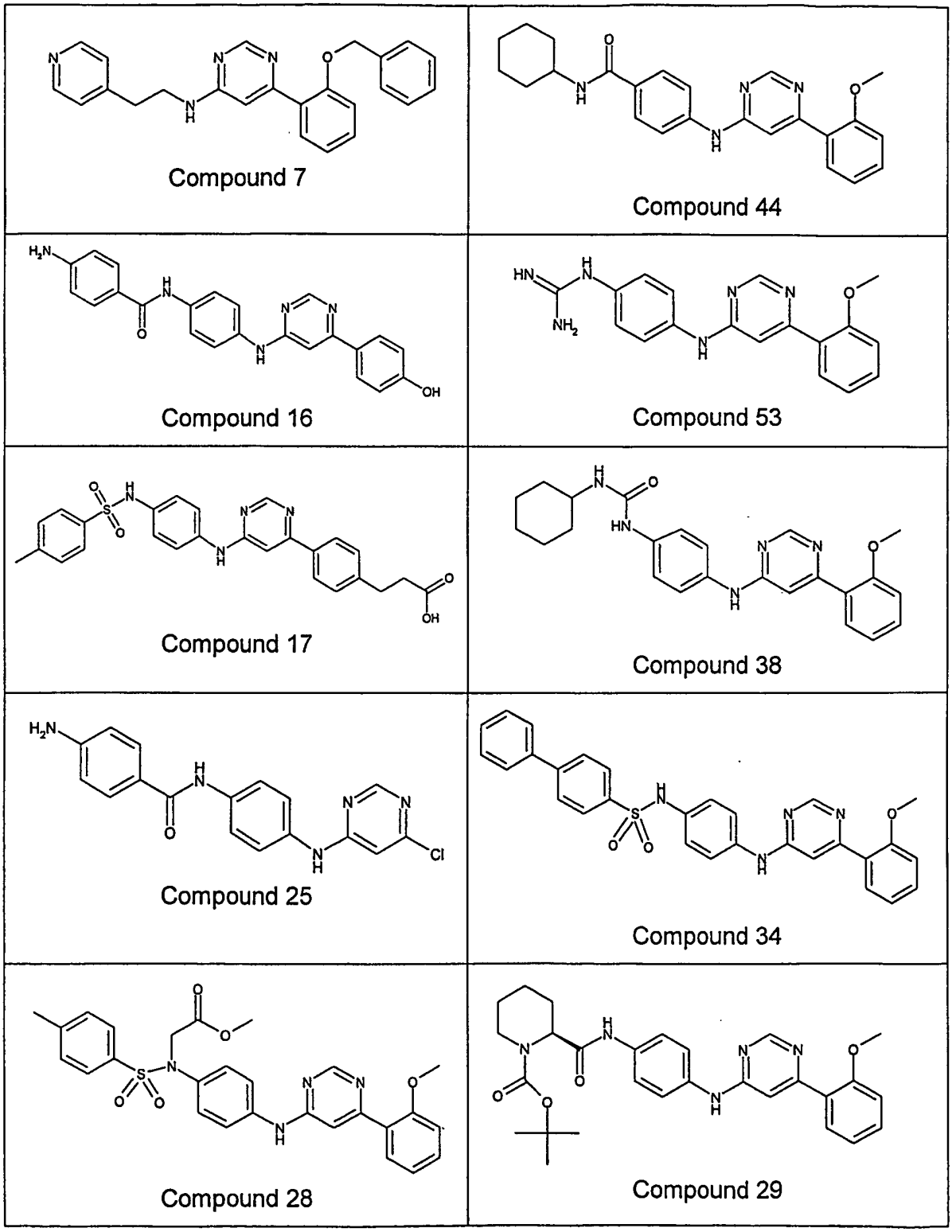
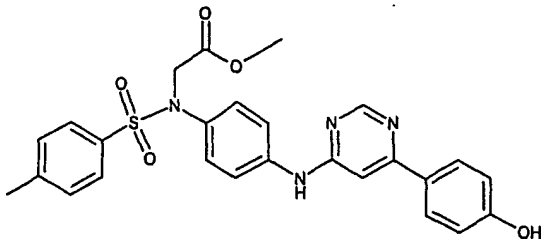
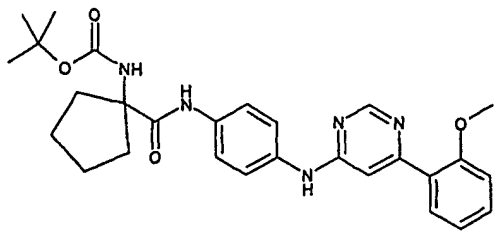


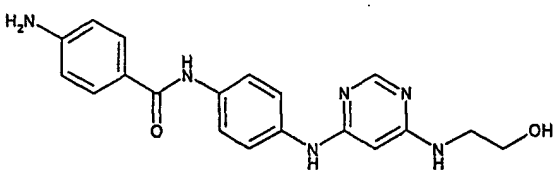
Figure 1b



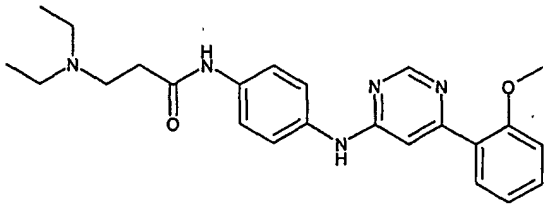
Compound 27



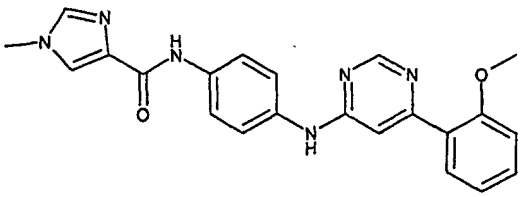
Compound 47



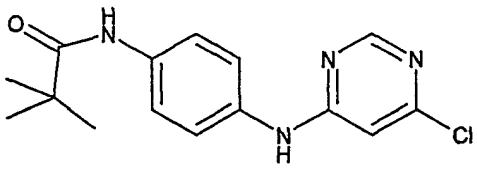
Compound 60



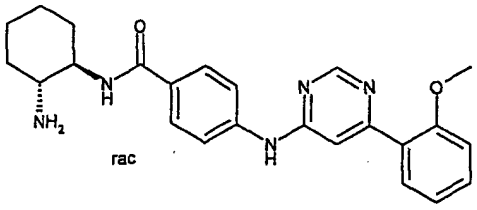
Compound 64



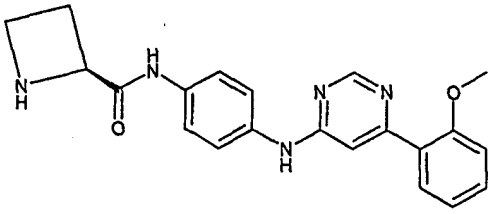
Compound 70



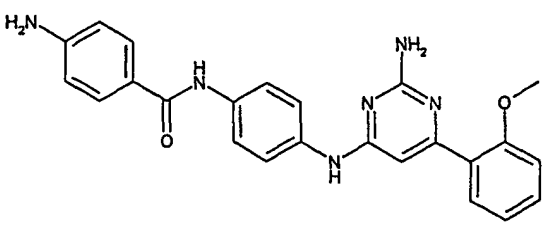
Compound 72



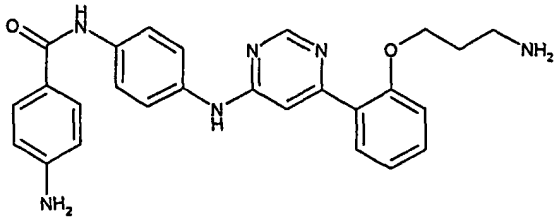
Compound 83



Compound 90



Compound 97



Compound 103

Figure 1c

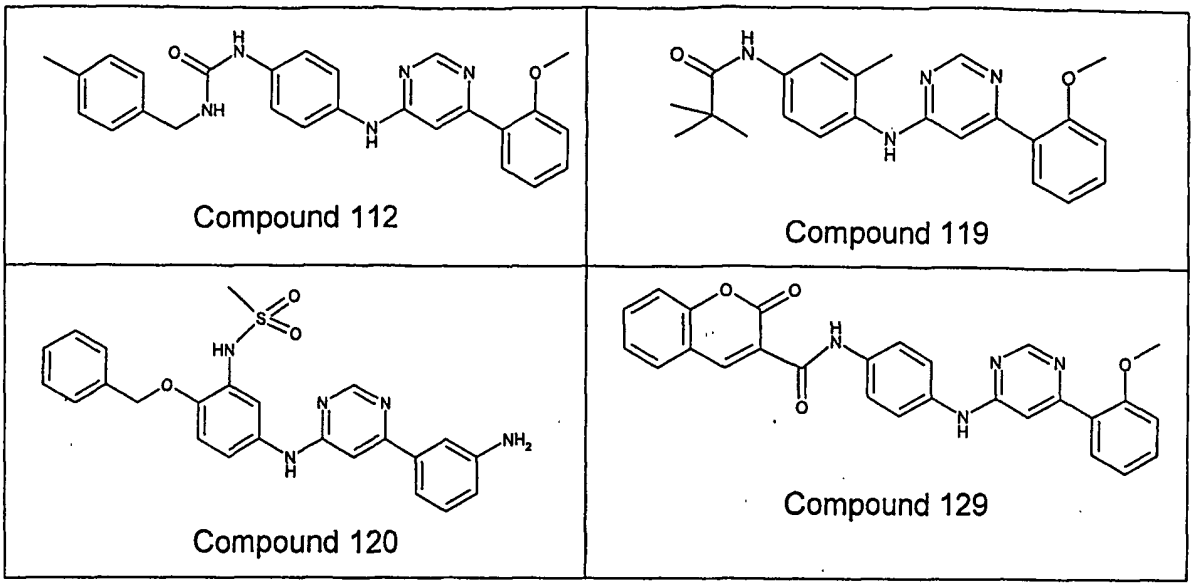


Figure 2

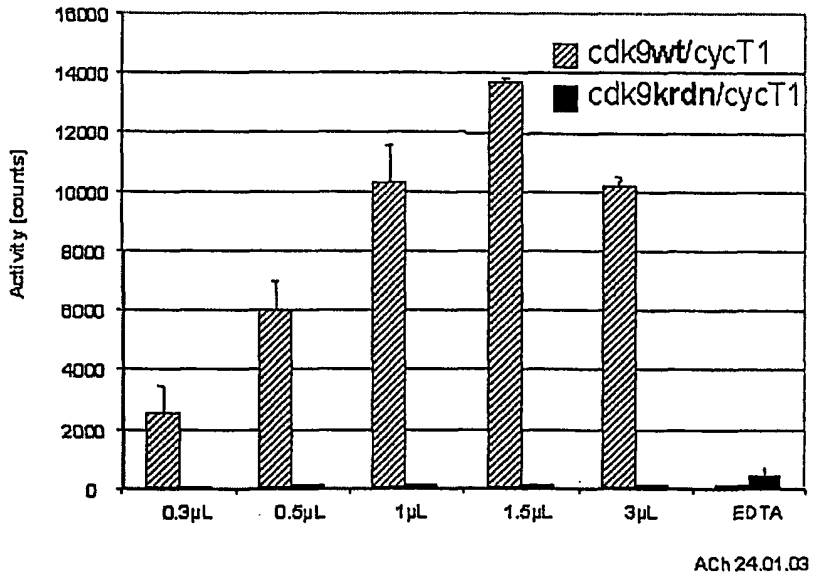


Figure 3

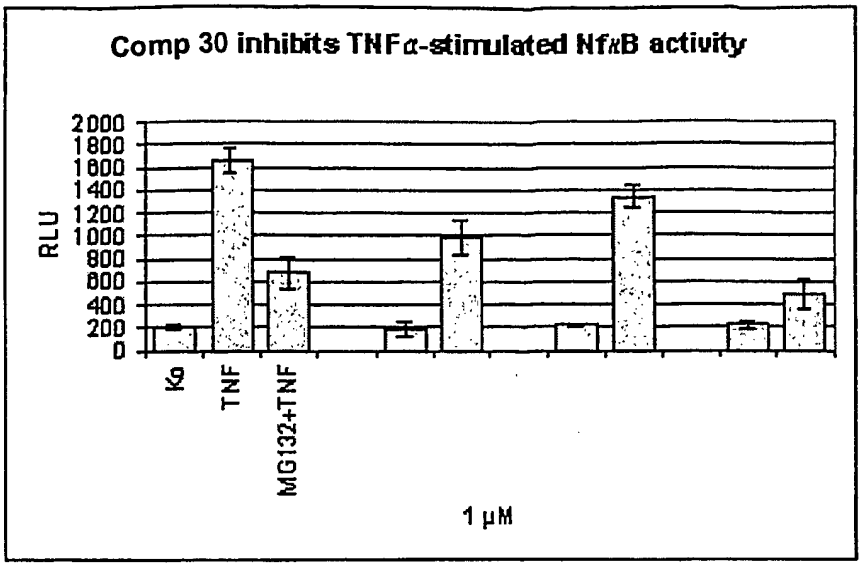


Figure 3: Effect of compounds on dependent NFκB-transcriptional activity,

Figure 4

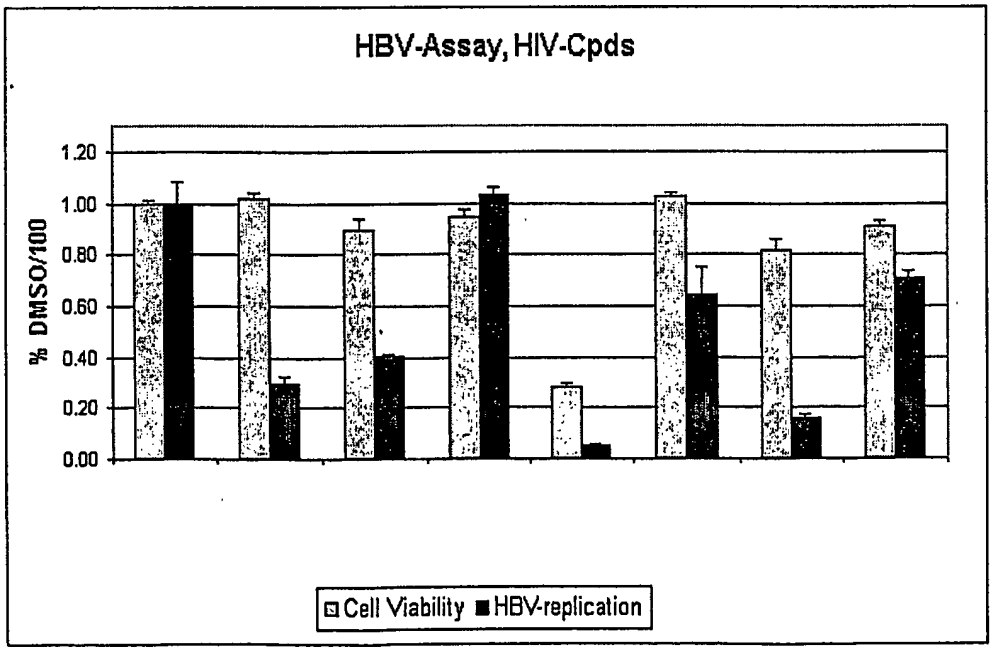
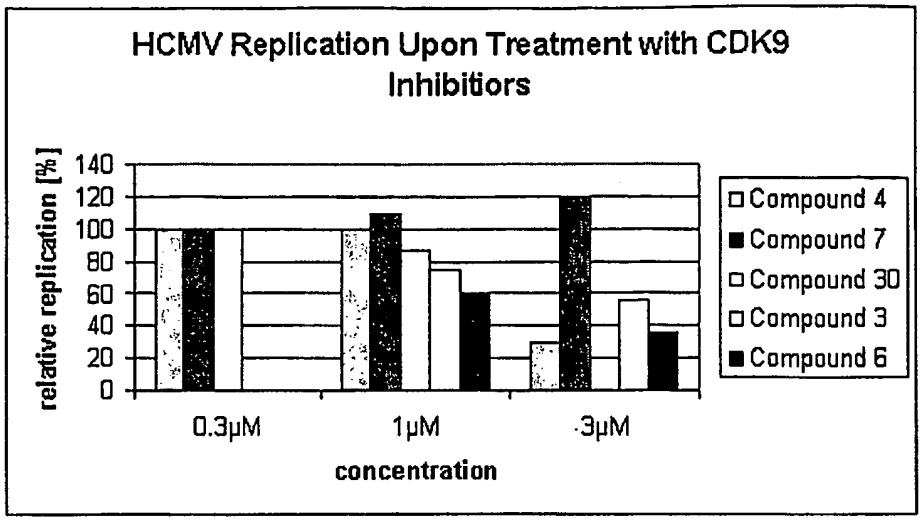


Figure 4: Effect of compounds on HBV replication

Figure 5

HCMV replication



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/010353

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/42 C07D401/12 C07D239/48 C07D403/12 C07D401/04
C07D409/12 C07D417/12 C07D405/12 C07D409/14 C07D413/12
C07D409/04 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 168 262 A (FUJISAWA PHARMACEUTICAL CO) 15 January 1986 (1986-01-15) example 33	1,9,17
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X	US 3 950 525 A (DE ANGELIS GERALD GEORGE ET AL) 13 April 1976 (1976-04-13) example VIII	1,9,17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
5 January 2005	18/01/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fanni, S

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EL-REEDY A M ET AL: "AZOLOPYRIMIDINES AND PYRIMIDOQUINAZOLINES FROM 4-CHLOROPYRIMIDINES" JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US, vol. 26, no. 2, 1989, pages 313-316, XP000929372 ISSN: 0022-152X example VIII	1,9,17
X	FALCH E ET AL: "SUBSTITUTED HETEROAROMATIC ANTHRANILIC ACIDS WITH ANTIINFLAMMATORY ACTIVITY" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 11, no. 3, May 1968 (1968-05), pages 608-611, XP001069203 ISSN: 0022-2623 table I	1,9,17
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